



सत्यमेव जयते
Ministry of Health & Family Welfare
Government of India



A Comprehensive Learning Guide

Scrub Typhus



**NATIONAL CENTRE FOR DISEASE CONTROL
DIRECTORATE GENERAL OF HEALTH SERVICES**
Ministry of Health & Family Welfare, Government of India



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Scrub Typhus

A Comprehensive Learning Guide

Centre for One Health

National Centre for Disease Control
Directorate General of Health Services
Ministry of Health & Family Welfare
Government of India

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स्वास्थ्य सेवा महानिदेशालय

Government of India
Ministry of Health & Family Welfare
Directorate General of Health Services



Message

Zoonotic diseases pose a significant and ongoing threat to biodiversity, human and public health and economic stability. Given India's diverse ecosystem, high population density and increasing human-animal action, the country remains particularly susceptible to zoonotic outbreaks. Past occurrences of plague, Nipah virus, avian influenza, leptospirosis, and Kyasanur Forest Disease emphasizes a critical need for robust surveillance, early detection, and a coordinated, intersectoral response.

Recognizing the importance of addressing zoonotic diseases as a public health priority, the Centre for One Health, under the National Centre for Disease Control (NCDC), is committed for strengthening surveillance, prevention, and response mechanisms through an integrated One Health approach. As part of this effort, the Centre for One Health has developed comprehensive learning guides on Priority Zoonotic Diseases. These modules provide scientifically validated, evidence-based guidance on the epidemiology, diagnosis, treatment, and prevention of key zoonotic diseases.

Strengthening disease surveillance, ensuring early diagnosis, and implementing timely interventions through a coordinated and multi-sectoral approach are critical to mitigating the risks associated with zoonotic diseases.

I am pleased to release these learning guides as a significant step in our ongoing efforts to combat zoonotic diseases. I urge all healthcare professionals, veterinary experts, and community leaders to actively utilize these resources to enhance their clinical index of suspicion for zoonosis and eventually contribute towards strengthening our health care system for responding timely and more efficiently to future outbreaks.

(Atul Goel)



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MESSAGE

It is my pleasure to know that the Centre for One Health at NCDC has prepared **Comprehensive Learning Guides** on 10 priority zoonotic diseases, which is now being shared with all concerned.

These resources become relevant in considering; India has encountered multiple zoonotic disease outbreaks in recent years, highlighting their persistent and evolving threat to public health. The re-emergence of **Nipah virus** in Kerala, **Kyasanur Forest Disease (KFD)** in Karnataka, and **avian influenza** across several states underscores the complex interconnections between human, animal, and environmental health. The rising cases of **leptospirosis** and **scrub typhus**, driven by climatic changes and ecological disruptions, further illustrate the unpredictable nature of zoonotic spillovers. With the additional challenges posed by **emerging coronaviruses** and **antimicrobial resistance (AMR)**, there is an urgent need for a **cohesive, evidence-based approach** to mitigate these risks effectively.

In recognition of this pressing need, the **National Centre for Disease Control (NCDC)** has intensified its efforts to fortify **zoonotic disease surveillance, outbreak preparedness, and intersectoral coordination**. As part of this initiative, the **Centre for One Health, NCDC**, has meticulously curated **Comprehensive Learning Guides** on priority zoonotic diseases. These guides, underpinned by the latest scientific insights and global best practices, serve as indispensable resources for **healthcare professionals, veterinarians, and epidemiologists**, equipping them with the knowledge to anticipate, detect, and mitigate zoonotic threats with precision.

To effectively curtail the impact of zoonotic diseases, a **harmonized One Health approach** is paramount—one that transcends disciplinary boundaries and fosters synergies across the human, animal, and environmental health sectors. I urge all stakeholders to **leverage these scholarly resources, enhance disease intelligence networks, and champion research-driven interventions**. By embracing a proactive and interdisciplinary ethos, we can **bolster pandemic preparedness, fortify national health security, and avert future spillover events**.

I sincerely **appreciate** my colleagues at the Centre for One Health, NCDC for their dedication to strengthening zoonotic disease control. Their efforts in enhancing surveillance, preparedness, and public health response are crucial in preventing and managing emerging health threats.

I am glad to see their commitment translating into evidence-based interventions and capacity-building initiatives that enhance zoonotic disease surveillance, outbreak preparedness, and overall health system resilience.

Through continuous innovation, collaboration, and unwavering dedication, we can fortify our health systems and safeguard our nation against zoonotic threats.

Wishing you all happy learning and skill enhancement wherever possible.

रंजन दास 19/3/25

Prof. (Dr.) Ranjan Das



Antibiotic resistance Containment Stewardship: Our Role, Our Responsibility
Judicious Use of Antibiotic: Key to Contain Antibiotic Resistance





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Message

Zoonotic diseases of public health importance continue to pose significant challenges to public health. These diseases, often driven by intricate human-animal-environment interactions, present substantial health risks, particularly to vulnerable populations, and demand a coordinated and robust response from the health sector.

In recognition of the pivotal role healthcare providers play in addressing these challenges, the **Centre for One Health** has developed a **Comprehensive Learning Guide for Priority Zoonotic Diseases**. This guide is designed to build capacity across the health sector, equipping professionals with the essential knowledge and skills needed to identify, manage, and prevent these diseases effectively. By enhancing surveillance systems, fostering rapid and accurate diagnostics, and implementing targeted prevention and control measures, healthcare providers can play a transformative role in mitigating the impact of zoonotic diseases.

The guide emphasizes the importance of building a resilient health workforce capable of responding to outbreaks, engaging communities, and collaborating across disciplines. Through these efforts, we aim to reduce the burden of zoonotic diseases, improve health outcomes, and contribute to the creation of a safer and healthier future.

I encourage all healthcare professionals to utilize this guide as a resource for improving their understanding and response to zoonotic diseases. Together, let us strengthen our health systems and work towards a future free from the threats posed by zoonotic diseases.

Dr. Simmi Tiwari
Joint Director and Head
Centre for One Health



Antibiotic Resistance Containment Stewardship: Our Role, Our Responsibility
Judicious Use of Antibiotic: Key to Contain Antibiotic Resistance



Acknowledgement

The **Comprehensive Learning Guide** for Scrub Typhus has been developed to address the significant public health challenges posed by zoonotic diseases, which have serious health, economic, and social implications, particularly for vulnerable populations. The priority zoonotic diseases necessitate robust surveillance, timely diagnosis, and effective prevention and control measures. This guide aims to strengthen the capacity of healthcare professionals by equipping them with the requisite knowledge and skills to mitigate these public health threats and improve health outcomes.

We acknowledge with deep appreciation the valuable contributions of the **subject matter experts** from leading medical institutions and research organizations, whose guidance and technical expertise has been critical in shaping this **Comprehensive Learning Guide**.

The Centre for One Health, NCDC, expresses its sincere gratitude to Ms. Punya Salila Srivastava, Secretary, Health and Family Welfare, Government of India; Ms. L.S. Changsan, Additional Secretary, Ministry of Health and Family Welfare, Government of India; Prof. (Dr.) Atul Goel, Director General of Health Services (DGHS), Government of India; Ms. Latha Ganapathy, Joint Secretary, Department of Health & Family Welfare, Government of India for their leadership, guidance, and support.

Lastly, we acknowledge the USAID-funded RISE project team, implemented by Jhpiego, for their technical support in drafting and finalizing this guide. Their collaboration has been pivotal in ensuring the quality and relevance of this resource.

Dr. Simmi Tiwari
Joint Director and Head
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Preface

Scrub typhus, caused by *Orientia tsutsugamushi* bacterium, is a potentially life-threatening infectious disease transmitted through the bites of infected chiggers. This often-overlooked vector-borne illness presents a significant public health challenge, necessitating a deeper understanding and heightened awareness for effective prevention and management.

This training module aims to equip learners with the knowledge and tools necessary to educate and train individuals involved in various aspects of Scrub Typus management. It provides a comprehensive overview of the disease, covering its epidemiology, clinical presentation, laboratory diagnosis, treatment availability, and preventive measures. The module is structured in a user-friendly manner, allowing learners to effectively communicate complex scientific concepts to their audience. It contains detailed explanations to enhance understanding and engagement. The content is supported by the latest scientific research and public health guidelines, ensuring the information presented is accurate and up to date.

It is our sincere hope that this module will serve as a valuable resource for learners and educators, enabling them to grasp essential knowledge and skills. By equipping professionals and individuals at risk with the necessary information, we can enhance our collective ability to detect, prevent, and respond to Scrub Typus outbreaks, thereby safeguarding public health.

We would like to express our gratitude to all the experts, researchers, and contributors who have provided their invaluable insights and expertise in developing this scientific module. Their dedication and commitment to public health have been instrumental in creating a comprehensive resource that will contribute to the effective management of Scrub Typus.

We hope you find this module informative, engaging, and ultimately, empowering. Together, let us work towards building a safer and healthier future by combating Scrub Typus through knowledge and preparedness.

Abbreviations

AES	Acute Encephalitis Syndrome
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
BHK	Baby Hamster Kidney (Cell Line)
BSL	Biosafety Level
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CHC	Community Health Centre
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
DEET	N,N-Diethyl-meta-toluamide (Insect Repellent)
DIC	Disseminated Intravascular Coagulation
DNA	Deoxyribonucleic Acid
EWS	Early Warning Signal
ELISA	Enzyme-Linked Immunosorbent Assay
ESR	Erythrocyte Sedimentation Rate
ICMR	Indian Council of Medical Research
IDSP	Integrated Disease Surveillance Programme
IEC	Information, Education, and Communication
IFA	Immunofluorescence Assay
IFAT	Indirect Fluorescent Antibody Test
IGG	Immunoglobulin G
IGM	Immunoglobulin M
IGRA	Interferon-Gamma Release Assay
LFF	Low-Frequency Filter
LPS	Lipopolysaccharide
OX ANTIGEN	OX Series Antigens (OX2, OX19, OXK)
PCR	Polymerase Chain Reaction
PHC	Primary Health Centre
PT	Prothrombin Time
RRT	Rapid Response Team
TB	Tuberculosis
TSA56	Tsutsugamushi Antigen 56

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Introduction to Learning Guide for Scrub Typhus

Historically, zoonotic diseases have had a significant impact on human evolution, particularly on cultures and societies that domesticated and raised animals for food and clothing. Zoonoses pose a frequent and feared risk to humanity, transcending natural boundaries and occurring worldwide. Their profound effect on the global economy and health is well recognized, ranging from the international movement of animals and the importation of diseases to bans on animal product imports and restrictions on other international trade practices. Thus, zoonoses are no longer confined to national borders, and global surveillance is necessary for effective control.

Controlling zoonoses remains a priority for international agencies, addressing the specific health and economic challenges of each region. They equally impact animal, human, and environmental sectors, causing substantial damage to the nation's economy. To protect all the sectors, it is essential to rapidly identify, diagnose, and manage these diseases. The One Health approach plays a crucial role in this endeavor, as we have learned valuable lessons from the COVID-19 pandemic regarding the need for strong surveillance and diagnostic preparedness to handle future pandemic situations.

To provide comprehensive training, the Center for One Health, NCDC has developed a Comprehensive Learning Guide. This guide serves as both trainers' guides and self-directed learning resources. The training focuses on zoonoses and zoonotic diseases of public health importance in India (ZPHI) and emphasizes the One Health approach to responding to zoonotic diseases. By the end of the training, participants should have a solid understanding of the core principles of Scrub Typhus, its outbreak potential, health emergencies, risk communication, diagnostic procedures, laboratory safety, surveillance, data reporting, and their applications.

The LRPs are based on national and international guidelines and serve as a comprehensive training resource for individuals involved in zoonotic disease diagnosis and surveillance activities. The curriculum is designed to enable facilitators and learners to undergo step-by-step learning within a specified time frame, ensuring a thorough understanding of each module. The LRPs cater to various audiences, including medical professionals including doctors, veterinarians, paramedical staff and laboratory personnel who are expected to acquire knowledge and competencies beyond their regular field of work.

The LRP consists of a Facilitators' Guide (FG) The FG provides instructional processes and supports educators in facilitating and assessing learning. Each module follows a standardized structure, including a session outline, detailed session plans, slide decks, and a wide range of references and resources for further reading. These resources offer comprehensive information on the respective topics.

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COURSE DESCRIPTION

Course Design

This comprehensive Scrub Typhus training guide is tailored for medical professionals including doctors, paramedical staff, and laboratory personnel. The course is designed to enhance their understanding and expertise in dealing with Scrub Typhus cases, spanning various aspects of prevention, diagnosis, and treatment. The training approach emphasizes practical application, aiming to equip participants with hands-on skills and competencies that can be directly applied in their professional roles.

Evaluation Approach

The evaluation approach for the Scrub Typhus preparedness and response guide includes a comprehensive pre- and post-training quiz questionnaire designed to assess participant's knowledge and learning progression. The questionnaire utilizes multiple-choice questions (MCQs) to gauge participant's understanding of Scrub Typhus disease before and after the training. This approach allows a clear measurement of knowledge enhancement and provides valuable insights into the effectiveness of the training program.

- ***Pre-Training Quiz:***

Before the training begins, participants will undergo a pre-training questionnaire. This questionnaire serves as a baseline assessment of participant's existing knowledge and awareness of Scrub Typhus. The pre-training quiz will consist of MCQs that cover various aspects of Scrub Typhus, including its etiology, modes of transmission, clinical manifestations, preventive measures, and response strategies. The purpose of the pre-training quiz is to establish a starting point and identify areas where participants may require more focused training.

- ***Post-Training Quiz:***

Upon completion of the Scrub Typhus preparedness and response training guide, participants will be given a post-training quiz questionnaire. This questionnaire will contain a similar set of MCQs as the pre-training quiz, covering the same topics related to Scrub Typhus. The aim of the post-training quiz is to evaluate participant's knowledge advancement and to measure the effectiveness of the training in enhancing their understanding of Scrub Typhus.

COURSE SYLLABUS

Course Goals

- Foster an in-depth comprehension of Scrub Typhus and its diverse forms.
- Equip participants with skills for Scrub Typhus diagnosis, management, and prevention.
- Emphasize the importance of the One Health approach in addressing zoonotic diseases.
- Develop proficiency in risk associated with the disease, laboratory safety, and surveillance strategies.

Participant's Learning Objectives

By the course's conclusion, participants will be able to:

- Identify various Scrub Typhus forms and their clinical characteristics.
- Apply diagnostic and treatment protocols for Scrub Typhus management.
- Implement preventive strategies and outbreak management strategies.

Participant Selection Criteria

Participants for the Scrub Typhus response and preparedness training should be professionals from various fields involved in emergency response and public health:

- Emergency Responders: Including public health experts, medical personnel, and first responders.
- Laboratory and Biosafety Staff: Those experienced in handling biohazards.
- Government and Decision-Makers: Officials with authority in emergency coordination.
- Community Leaders and Experts: Community influencers, researchers, and mental health specialists.

Using the Resource Guide

All training activities in this course will be conducted in an interactive, participatory manner using the training guide appropriately as suggested in the course outline in the facilitator's guide. To accomplish this, the trainer will have to change roles throughout the course. For example, the trainer is a facilitator when conducting small group discussions and finally, when objectively assessing performance, the trainer serves as an evaluator.

Composition of participants

The training is intended for 15-20 participants hailing from various state and healthcare fraternities. There can be a single facilitator as an expert of the disease.

COURSE SCHEDULE

Morning Session

Introduce and welcome participants

- Discuss participant expectations and prior knowledge
- Outline the objectives of the course and learning outcomes

Review the course schedule and its components

- Provide an overview of the training guide materials
- Conduct a pre-course knowledge assessment to gauge participants' baseline understanding
- Distribute course materials, including handouts and resources

Interactive presentations

- Take Sessions 1-4 and discuss in detail about basics of Scrub Typhus, its epidemiology and its significant features in humans and animals.
- Interactive discussion and Q&A session after the lecture

Afternoon Session

Interactive presentations

- Take Sessions 5-10 and discuss in detail about diagnosis of Scrub Typhus, its treatment, prevention & control, and its surveillance & outbreak management.

Debriefing and group discussions on simulation outcomes

- Interactive discussion and Q&A session after the lecture

Review, Assessment, and Closing

- Comprehensive review of key concepts covered during the training
- Interactive quiz to reinforce learning
- Final assessment to measure participants' understanding of course material
- Reflection session: Participants share insights and takeaways from the course
- Closing remarks, thanking participants for their engagement

COURSE OUTLINE

The course outline presented here follows a model structure for the training curriculum. It delineates the enabling objectives necessary to achieve the participant learning goals outlined in the course syllabus. The outline offers recommendations for suitable learning activities and essential resources and materials for each enabling objective. Depending on specific participant requirements, the trainer has the option to introduce supplementary practice activities, devise case studies, role-play scenarios, or tailor learning situations accordingly.

The course outline comprises four columns:

- **Duration:** This column specifies the estimated time allocated for each learning activity. This allocation ensures an equitable distribution of time across the diverse training components.
- **Learning Objectives:** This column specifies the estimated time allocated for each learning activity. This allocation ensures an equitable distribution of time across the diverse training components.
- **Pre-requisite Knowledge/Skill:** This column addresses the foundational knowledge or skills that participants should possess prior to the session. It underscores the importance of existing competencies for effective engagement in the training.
- **Competencies to be Achieved:** The fourth column enumerates the competencies participants are expected to acquire by the conclusion of the session. It underscores the practical outcomes that participants will attain through engagement in the training.

AGENDA

S. No	Topic	Duration
1.	Welcome & Introduction of the training agenda and setting ground rules	15 mins
2.	Ice Breaker: Talk about yourself - Contribution to the management & control of zoonoses - Expectations from the training	30 mins
3.	Training objectives	15 mins
4.	Pre-Test Quiz	20 mins
5.	Session 1: Introduction to Scrub Typhus	15 mins
6.	Session 2: Epidemiology	15 mins
7.	Session 3: Scrub Typhus in Human	15 mins
8.	Session 4: Scrub Typhus in Human	15 mins
9.	Session 5: Diagnosis	30 mins
10.	Session 6: Prevention & Treatment	15 mins
11.	Session 7: Surveillance and Outbreak Management	30 mins
14.	Post - Test Quiz	20 mins
15.	Q/A session, review, and discussion	15 mins
16.	Closing remarks	05 mins

Session-1

Introduction to Scrub Typhus

Course No. 001	Session 1: Introduction to Scrub Typhus
Duration	15 minutes
Learning Objective	• Describe disease overview • Understand causative agent and its characteristics • Understand factors affecting the disease incidence
Pre-requisite knowledge/skill	• Basic knowledge of rickettsial diseases and their transmission. • Familiarity with microbiological characteristics of pathogens and vector-borne infections. • Awareness of ecological and environmental factors influencing disease incidence and spread.
Competencies to be achieved	• Learners would gain knowledge of the basic characteristics and features of Scrub Typhus • Understanding of the characteristics of the causative agent • Describing the transmission cycle and factors associated with the disease

SCRUB TYPHUS: A CLOSER LOOK

Scrub Typhus is a disease that can affect humans when they are bitten by infected chiggers, which are the larvae of a small insect belonging to *Leptotrombidium delicense*. The disease is caused by a microorganism known as *Orientia tsutsugamushi*, which is a Gram-negative, obligate intracellular coccobacillus bacteria. Interestingly, traditional Gram staining method is not very effective for staining this bacterium, but more reliable results can be obtained using Giemsa and Gimenez stains. Giemsa staining results in a dark purple coloration of *Orientia*, while Gimenez staining yields a pale greenish-blue appearance. The disease's arthropod reservoir, the larval trombiculid mites (chiggers), can be found in a wider range of habitats than the name "scrub" might imply. Primary reservoir hosts for the disease are reported to be mice, rats, voles, shrews, and squirrels.

Orientia tsutsugamushi is an obligate intracellular bacterium that infects various types of cells, including monocytes, macrophages, dendritic cells, and endothelial cells. It spreads through the bloodstream and lymphatic systems. It resides within trombiculid mites and possesses a single circular chromosome ranging from 1.93 to 2.47 megabases in size, with no known plasmids. Its genome contains between 2086 and 2709 predicted genes, with a core set of 657 genes. Notably, it has one of the most highly repetitive bacterial genomes known, with nearly half of the genome consisting of repetitive DNA elements. It lacks lipopolysaccharides (LPS) and has a minimal peptidoglycan-like structure in its cell wall.

The bacterium encodes multiple effector proteins containing ankyrin-repeat motifs that interact with host cell pathways. Its outer membrane is predominantly composed of the highly abundant surface protein TSA56, which has variable domains that differ between strains and plays a crucial role in serological diagnostics and as a candidate for vaccine development. The doubling time for *Orientia tsutsugamushi* is approximately 8 to 9 hours. Currently, this microorganism is genetically challenging to manipulate or study in the laboratory.



Fig 1. *Orientia tsutsugamushi* cell from electron microscope

(Image source: https://pubmlst.org/static/organisms/orientia-tsutsugamushi/Orientia_tsutsugamushi_information.pdf)

KEY FACTORS CONTRIBUTING TO THE RISING INCIDENCE OF INFECTIOUS DISEASES

Key factors that contribute to the rising incidence of diseases. These factors highlight various environmental, demographic, and medical influences that collectively increase the spread and prevalence of infectious diseases:

- 1. Increased Urbanization:** Expanding urban areas lead to changes in land use, which disrupts ecosystems and increases contact between humans and disease-carrying organisms (vectors), potentially leading to higher disease transmission rates.
- 2. Population Explosion:** Rapid growth in human populations pushes people into areas where disease vectors (such as mosquitoes or rodents) are more common, increasing the likelihood of vector-borne diseases spreading.
- 3. Availability of Diagnostic Tests:** Improved diagnostic capabilities enable more frequent and accurate testing, which results in better reporting and tracking of disease cases. This can lead to a perceived rise in disease incidence as more cases are detected and recorded.
- 4. Change in Antimicrobial Prescription Practices:** Overuse or misuse of certain newer antibiotics (such as fluoroquinolones and third-generation cephalosporins) has reduced their effectiveness. Older antibiotics (like chloramphenicol and tetracyclines) may sometimes prove more effective for empirical treatment, but their reduced use has contributed to antimicrobial resistance, complicating treatment options.
- 5. Climate Change and Global Warming:** Rising global temperatures and other climate changes alter the habitats of disease vectors, allowing them to thrive in new areas. This shift can lead to the spread of vector-borne diseases to regions previously unaffected by these vectors.

Scrub Typhus is a zoonotic disease caused in humans when bitten by infected Chiggers (a larvae of a small insect from the family of *Leptotrombidium delicense*).



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SCRUB TYPHUS

Scrub Typhus is caused by a Rickettsial organism *Orientia tsutsugamushi*, which is a gram negative, obligate, intracellular, coccobacilli organism



Center for the Study of Health, NCHC, 30017

SCRIB. TYPHUS

- *Orientia tsutsugamushi*, the bacterium responsible for scrub typhus, can be effectively stained with Giemsa or Gimenez stains. The Giemsa stain is preferred, as it colors *Orientia* a dark purple, while Gimenez stain gives it a pale greenish-blue appearance.



• The *Orientia tsutsugamushi* genome is a single circular chromosome, ranging from 1.93 to 2.47 million base pairs (Mb) in size, with no plasmids. It has 2,086 to 2,709 predicted genes, including a core set of 657 essential genes.



• The disease is transmitted by larval trombiculid mites, or chiggers found in a wide range of habitats beyond just scrublands. Small animals such as mice, rats, voles, shrews, and squirrels are the primary reservoirs carrying it and spreading the infection to new areas.

Center for the Study of Health, WISC: M2070

SCRIPT TYPINGS

Increased urbanisation (resulting in changing land use patterns)



Population explosion (human expansion to vector areas)



Availability of specific diagnostic tests (inc. testing and inc. reporting)



Change in antimicrobial prescription practices (fluoroquinolones and second and III gen Cephalosporins have been ineffective as compared to chloramphenicol and tetracyclines for empiric treatment)



Climate change - Global warming (shift in vector distribution)

Center for the Study of the History of Mathematics

SCRUB TYPHUS

[illegible]

Session-2

Epidemiology of Scrub Typhus

Course No. 002	Session 2: Epidemiology of Scrub Typhus
Duration	15 minutes
Learning Objective	• Understand history of Scrub Typhus emergence • Understand geographical distribution of Scrub Typhus globally • Understand the disease transmission
Pre-requisite knowledge/skill	• Basic understanding of historical trends in infectious disease emergence. • Familiarity with global and regional distribution of vector-borne diseases. • Awareness of transmission cycles involving vectors, reservoirs, and humans.
Competencies to be achieved	• Knowledge of the source of infection • Understanding of the disease transmission • Assessment of geographical distribution and prevalence of Scrub Typhus disease

EPIDEMIOLOGY

Scrub Typhus is prevalent in a variety of geographical regions, including sandy beaches, mountain deserts, and equatorial rainforests. Notably, specific environmental settings, such as forest clearings, riverbanks, and grassy areas, create ideal conditions for the infected mites that transmit scrub typhus to thrive. These localized high-risk regions for human infection have been referred to as "Scrub Typhus Islands."

The infection is transmitted through the larval mites or 'chiggers' belonging to the family *Trombiculidae*. Notably, only the larval stages of these mites feed on blood. The natural hosts for scrub typhus are small rodents, with a particular emphasis on wild rats of the subgenus *Rattus*. These rodents serve as reservoirs for the disease, and the vector mites play a crucial role in perpetuating the infection in nature.

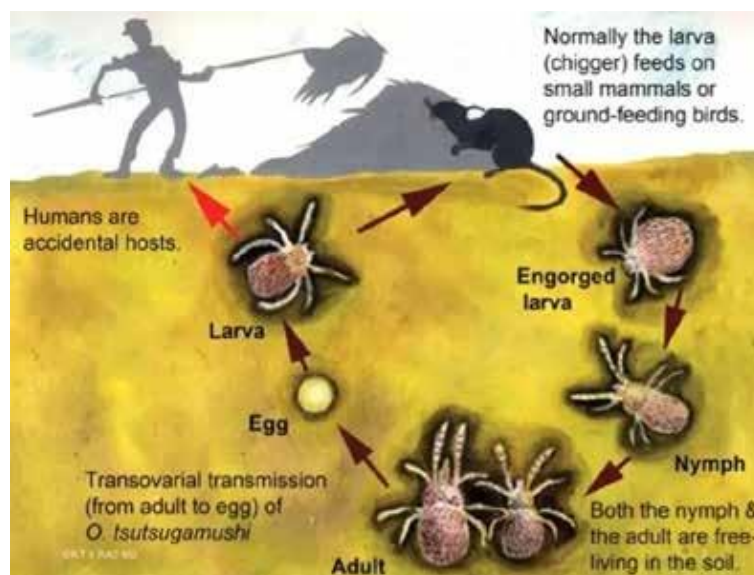


Fig 2. Life cycle of mite and transmission dynamics of *Orientia*

(Image source: https://microbeonline.com/scrub-typhus-overview-pathogenesis-and-lab-diagnosis/#google_vignette)

These vector mites are known to inhabit diverse ecological niches, spanning from equatorial rainforests to semi-desert regions and even Alpine subarctic terrains in the Himalayan regions. Endemic foci of scrub typhus are often associated with specific types of habitats. These include abandoned plantations, gardens, rice fields, overgrown forest clearings, shrubby fringes along the boundaries of fields and forests, riverbanks, and grassy fields. These ecological patches that attract the natural hosts of the mite vectors are often referred to as 'mite islands.' These unique ecological niches play a vital role in the transmission and persistence of scrub typhus within the affected regions.

The transmission of this disease varies depending on the geographical region. In tropical areas, scrub typhus can occur throughout the year, while in temperate zones, transmission is typically seasonal. Importantly, human-to-human transmission of scrub typhus is not reported. Infection occurs when individuals inadvertently come into contact with an infective larval mite while walking, sitting, or lying on the ground infested with these vectors. This mode of transmission underscores the importance of environmental factors and human behavior in the spread of scrub typhus.

About the Vector

Leptotrombidium deliense, a mite belonging to the Trombiculidae family, serves as a key vector in transmitting scrub typhus. In their larval stage, these mites, known as chiggers, attach to the host's skin and feed on blood. During this feeding process, infected larvae can transmit *Orientia tsutsugamushi*, the bacterium responsible for scrub typhus. Chiggers acquire this bacterium from previously infected hosts, perpetuating the disease cycle. These mites are commonly found in dense vegetation, such as scrublands and grassy areas, increasing the risk of exposure for humans and animals in these environments. The ability of *L. deliense* to thrive in such habitats makes it a significant health concern in areas prone to scrub typhus.

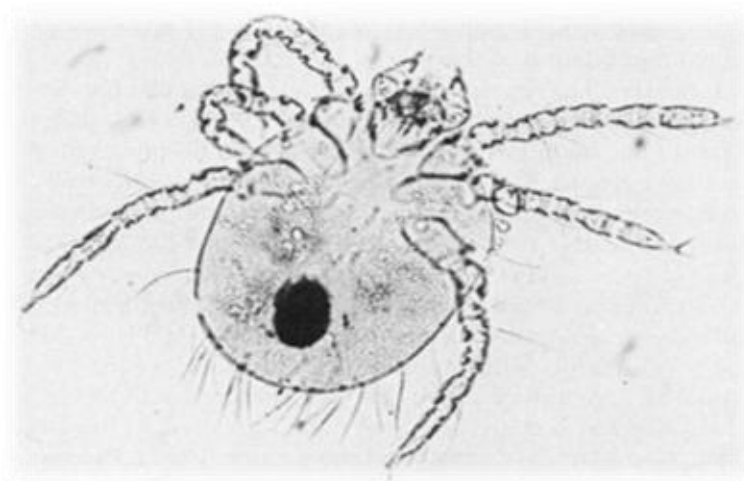


Fig 3. Chigger, larval stage of *Trombicula* sp.

(Image source - <https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/trombiculidae>)

Risk Factors

Understanding the risk factors for scrub typhus is essential for public health officials and healthcare providers in regions where the disease is endemic. These risk factors contribute to the increased prevalence and transmission of scrub typhus in certain areas.

Let's elaborate on each of these risk factors in more detail:

- 1. Increased Urbanization (Changing Land Use Patterns):** Rapid urbanization often leads to changes in land use patterns, including deforestation and alterations in natural habitats. These changes can disrupt the ecological balance and bring humans into closer contact with

the natural reservoir hosts, such as rodents, that carry the *Orientia tsutsugamushi* bacterium. This closer proximity increases the likelihood of transmission to humans.

2. **Population Explosion:** An increase in the human population can result in higher human-density areas. As more people live in close proximity, the chances of exposure to infected chiggers and rodents carrying scrub typhus increase. Overcrowded conditions and limited access to healthcare may also contribute to the spread of the disease.
3. **Climate Change:** Climate change can impact the distribution and activity of chiggers, which are the vectors responsible for transmitting scrub typhus. Altered temperature and humidity conditions can affect chigger populations and their ability to thrive, potentially expanding the geographical range of the disease.
4. **Human Behavior:** Certain human behaviors, such as trekking in endemic regions and visiting areas with a high prevalence of scrub typhus, increase the risk of exposure to chigger-infested environments. These mite islands, which are natural habitats for chiggers, become potential sources of infection when humans venture into these areas without taking preventive measures like using insect repellent or protective clothing.

Disease Burden

The global distribution of scrub typhus follows a distinctive pattern that is historically known as the "Tsutsugamushi triangle." This triangular area encompasses Afghanistan in the west and extends eastward to Japan and the Pacific region, including India and China. The triangle's northern boundary extends to Russia, while its southern boundary reaches the Philippines and Australia. Scrub typhus is endemic in India and can be found in various regions, including the Shivalik mountains stretching from Assam to Kashmir, the Eastern and Western Hills, and the Vindhya and Satpura mountain ranges in the country's central areas. Understanding the epidemiology and geographic distribution of scrub typhus is essential for healthcare professionals and researchers in effectively managing and preventing the disease.

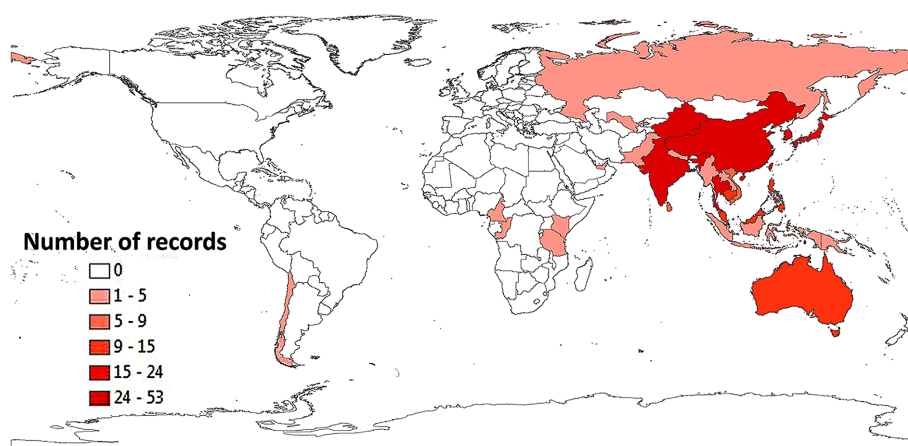


Fig 3. Map showing numbers of records by country of scrub typhus cases

(Image source: A Spatiotemporal Database to Track Human Scrub Typhus Using the Vector Map Application : December 2015 PLoS Neglected Tropical Diseases 9(12) DOI:10.1371/journal.pntd.0004161)

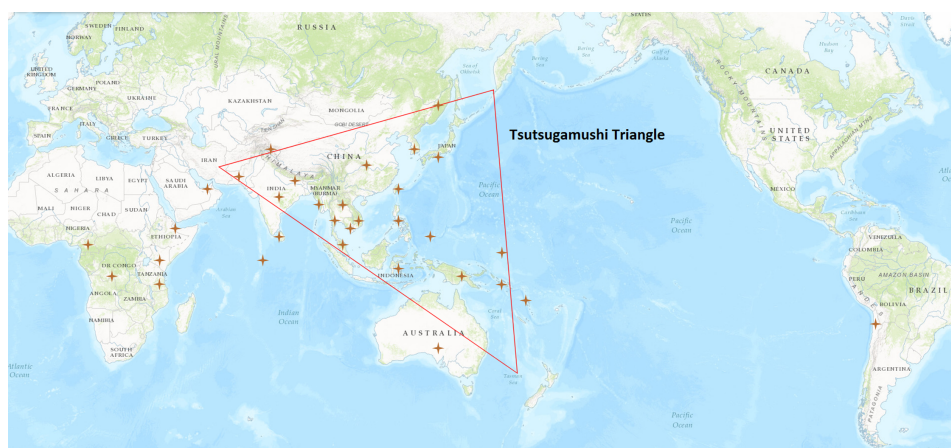


Fig 5. Worldwide map of countries with reported scrub typhus cases. The majority of scrub typhus cases occur in the “tsutsugamushi triangle” in the Asia-Pacific area. Countries with human cases are labeled with a star.

(Image source: A review of the global epidemiology of scrub typhus. *PLoS Negl Trop Dis* 11(11): e0006062. <https://doi.org/10.1371/journal.pntd.0006062>)

Table 1: Global Scrub Typhus Outbreaks

Country	Year(s)	Cases
India	2020	143
	2019	389
	2018	628
	2017	158
	2016	427
	2015	174
	2014	202
	2013	381
	2012	276
	2011	41
	2010	4
	1986	138
China	2005	32
	2011	45
	2012	29
Australia	1996-1997	28
	2000-2001	10
	2011	45
Japan	2000-2001	17
Maldives	2002-2003	17
Palau	2001-2003	15
Papua New Guinea	2001	39
Solomon Island	2014	9
Thailand	2002	17
	2006-2007	26

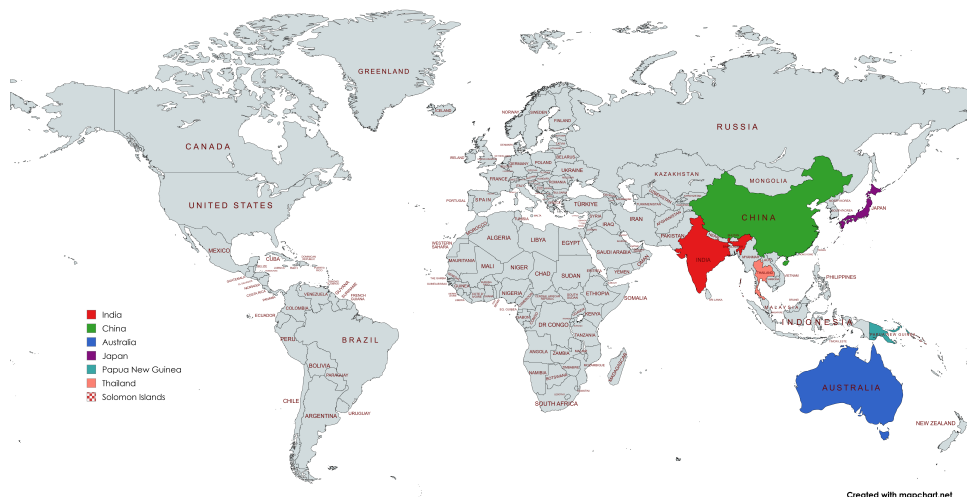


Fig 6. Global Scrub Typhus outbreak (mapchart.com)

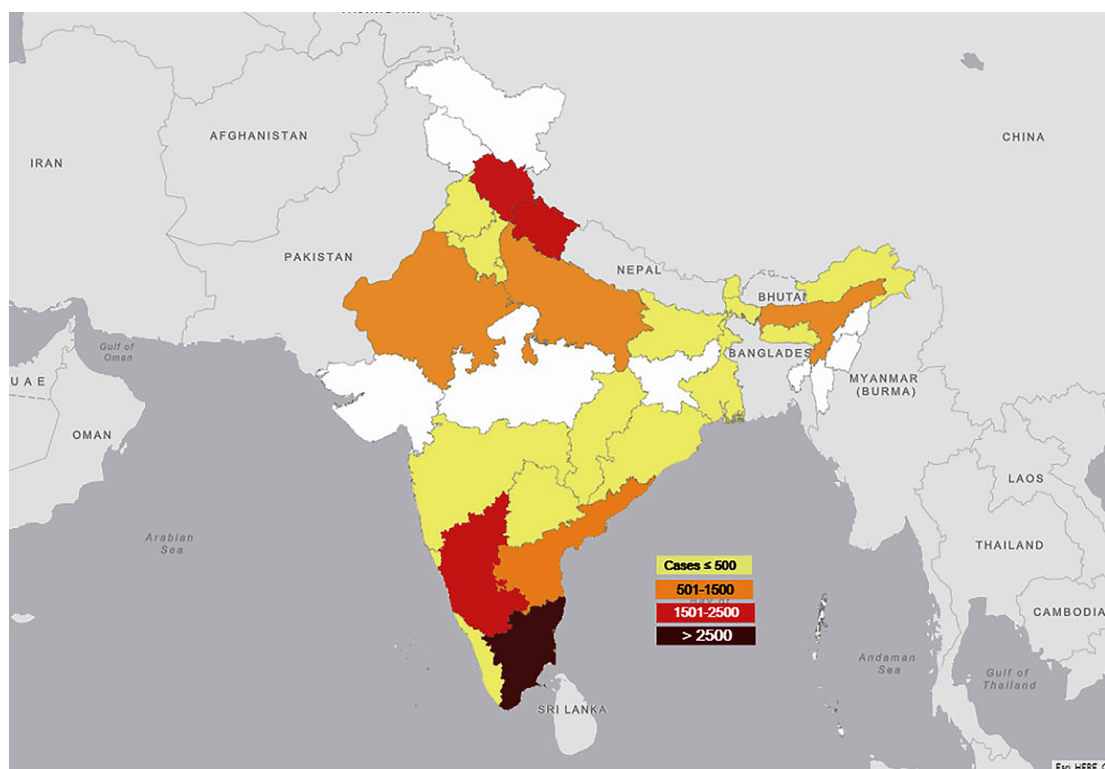


Fig 7. Mapping the regional distribution of scrub typhus in India.

Number of scrub typhus cases less than or equal to 500 is represented as yellow, 501–1500 cases is represented as orange, 1501–2500 cases is represented as red, and more than 2500 cases is represented as maroon.

(Image source: Regional distribution of Scrub typhus in India. PLoS Negl Trop Dis. 2021 Jul; 15(7): e0009619.)

Table 2: Scrub Typhus outbreaks in India

States	Year	Cases
Andhra Pradesh	2011-2012	176
	2013	258
Assam	2013-2014	228
Himanchal Pradesh	2004	21
	2010-2011	253
Jammu	2002	12
Kerala	2012	2
Manipur	2007	38
Meghalaya	2009-2010	24
	2010-2012	96
Odisha	2014-2015	25
	2011-2013	50
	2014	25
	2014-2015	40
	2015	71
	2015-2016	60
	2016-2017	10
	2017	201
	2020	240
Puducherry	2006-2008	50
	2011-2012	68
	2012-2013	28
Rajasthan	2012	42
Sikkim	2011	63
Tamilnadu	2001-2002	27
	2010-2012	95
Uttar Pradesh	2016	46
Uttarakhand	2013	69

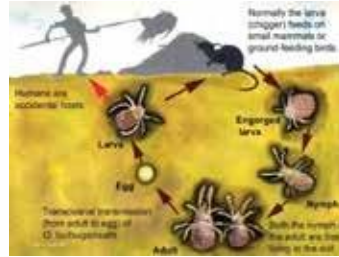


Fig 8. Scrub Typhus outbreaks in India

Source: An epidemiological outbreak of scrub typhus caused by *Orientia tsutsugamushi* – A comprehensive review *Journal of Applied Biology & Biotechnology* Vol. 10(5), pp. 76-83, Sep-Oct, 2022. Available online at <http://www.jabonline.in> DOI: 10.7324/JABB.2022.100509

Transmission Cycle

- The infection is transmitted to humans/animals through the bite of larval mites or "chiggers" (*Leptotrombidium deliense* and *Leptotrombidium akamushi*) which accidentally occurs while walking, sitting, or lying on the infested ground. Only the larval stage takes a blood meal.
- Human -to-human transmission is not reported.
- Disease pattern: bimodal pattern during the months of pre-monsoon and post-monsoon season with a peak in post-monsoon in human cases.



<https://microbeonline.com/scrub-typhus-overview-pathogenesis-and-lab-diagnosis/scrub-typhus/>

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SCRUB TYPHUS

Vector Properties

Family: Trombiculidae

Species: *Leptotrombidium deliense*

Larval mites (Chiggers) feed on blood during attachment to the host's skin.

Infected larvae can transmit *Orientia tsutsugamushi* during feeding.

They acquire the bacterium from infected hosts during **blood feeding**.

Found in dense vegetation: scrublands, grassy areas.



https://en.wikipedia.org/wiki/Chigger#/media/File:Chigger_mite.jpg

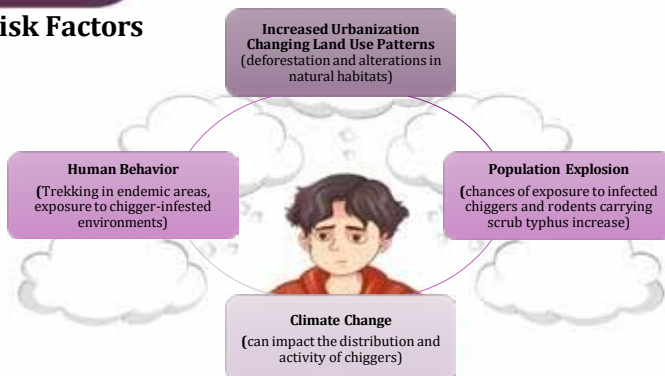


Source: <https://www.microbeonline.com/scrub-typhus-overview-pathogenesis-and-lab-diagnosis/scrub-typhus/>

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SCRUB TYPHUS

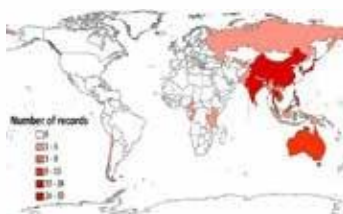
Risk Factors



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SCRUB TYPHUS

Disease Distribution



Disease Distribution (Global)



· The pattern of occurrence is enveloped within a triangle which is historically known as the *Tsutsugamushi triangle*.

· This triangle has its one angle on Afghanistan in the west and extends eastward till Japan and the Pacific region having India and China within its fold.

· The triangle has its second angle in the north till Russia and the last angle in the south till the Philippines and Australia.

Scrub Typhus Occurrence and the Tsutsugamushi triangle. Cases occur maximally within the Tsutsugamushi triangle. All countries reporting scrub typhus have been marked with a cross.

Source: A review of the global epidemiology of scrub typhus: PLOS NEGLECTED TROPICAL DISEASES

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SCRUB TYPHUS

Worldwide Scrub Typhus Outbreaks



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Source: A review of the global epidemiology of scrub typhus: PLoS Neg Trop Dis. 2017 Nov; 11(11): e0058062. Published online 2017 Nov 3. doi: 10.1371/journal.pntd.0058062

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SCRUB TYPHUS

Disease Distribution (India)



Source: Regional Distribution of Scrub typhus in India (Source: PLoS Neg Trop Dis. 2017 Jul; 11(7): e0168512)

· Scrub Typhus is endemic in India. It may be found in India's Shivalik mountains, which stretch from Assam to Kashmir, the Eastern and Western Hills, and the Vindhya and Satpura mountains in the Country's central area.

· Cases have been reported frequently from East (Bihar, West Bengal), West (Rajasthan, Maharashtra), North (Jammu and Kashmir, Himachal Pradesh, Uttarakhand), South (Andhra Pradesh, Karnataka, Tamil Nadu and Kerala), Central India (Delhi, Madhya Pradesh), North-east (Meghalaya, Assam, and Nagaland).

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SCRUB TYPHUS

Scrub Typhus Outbreaks in India



States	Year	Cases
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Odisha	2015-2016	60
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Source: An epidemiological outbreak of scrub typhus caused by Orientia tsutsugamushi – A comprehensive review. Journal of Applied Biology & Biotechnology Vol. 10(5), pp. 76-83, Sep-Oct, 2022. Available online at <http://www.jabonline.in> DOI: 10.7524/JAB.2022.100509

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SCRUB TYPHUS

Outbreaks were seen in the sub-Himalayan belt; from Jammu to Nagaland, mainly found in the whole Himalaya region ranging from Kashmir to Assam, Eastern and the Western Ghats, and the Vindhya and Satpura ranges in the central part of India. Outbreak occurred in Nagaland in 2014-2016

Notes

Session-3

Scrub Typhus in Human

Course No. 003	Session 3: Scrub Typhus in Human
Duration	15 minutes
Learning Objective	• Understanding the Clinical Manifestations • Understand the Disease Progression in Human
Pre-requisite knowledge/skill	• Basic understanding of human immune response to infectious diseases. • Familiarity with common symptoms of rickettsial infections. • Knowledge of complications and stages of disease progression in untreated cases.
Competencies to be achieved	• Knowledge of the disease transmission and clinical sign and symptoms in human.

SCRUB TYPHUS IN HUMANS

The clinical manifestations of scrub typhus are characterized by sudden onset of symptoms, including fever, often accompanied by the development of an eschar at the site where the mite bite. Clinical symptoms typically manifest after an incubation period of 6 to 21 days, with an average of 10 to 12 days. One distinctive feature of scrub typhus is the development of an eschar, which begins as a primary papular lesion and later evolves into a black ulcer with central necrosis. It's worth noting that the occurrence of this eschar may vary by region.



Fig 9. Clinical manifestations of Scrub Typhus

a) Maculopapular rash on back of a case of scrub typhus. b) Eschar of tick bite over the left side of the abdomen Symptoms

(Image source: https://www.researchgate.net/publication/328294454_CD_Alert_Scrub_typhus)

Eschar is noted in about 50-80% of the patients and is usually located in site as chest, abdomen, axilla, groin, and genitalia. Sometimes it may be seen on cheek, earlobe, and dorsum of the feet. The eschar, also known as 'touché noir,' is painless and may be missed if not specifically looked for. Patients may also experience chills, severe headache, and generalized lymphadenopathy. Notably, a pink to red macular rash, which does not merge and fades when pressure is applied, can be observed. The skin rash may develop within 3-8 days after the onset of fever. Besides these gastrointestinal symptoms may also be seen. If left untreated, scrub typhus can lead to complications such as interstitial pneumonia, meningoencephalitis, myocarditis, disseminated intravascular coagulation (DIC) and renal failure underscoring the severity of the disease. The organ involvement typically occurs in second week of illness. Scrub typhus with organ involvement is characterized as severe scrub typhus and carries higher mortality rate (an average of 24%). Scrub typhus in pregnancy is associated with poor maternal and fetal outcome. Approximately a third of pregnancies may result in either abortion or still birth.

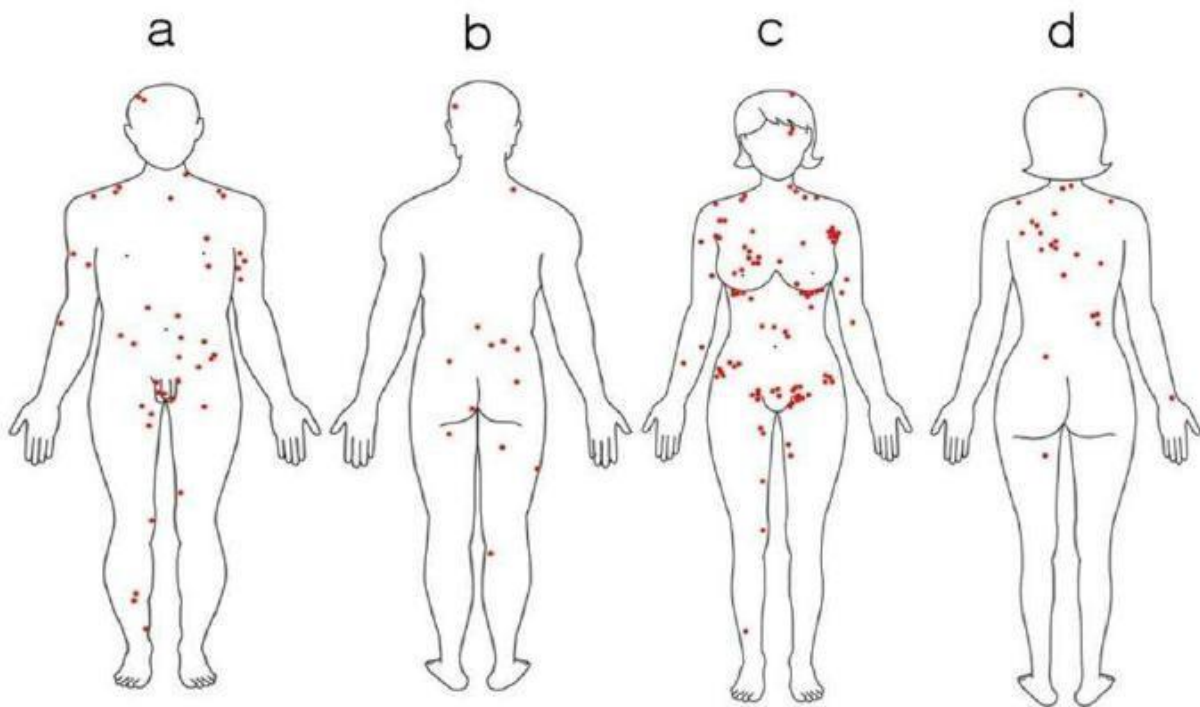


Fig 9. Sites that manifest an eschar in scrub typhus patients. a) male front; b) male back; c) female front; d) female back.

(Image source: Distribution of eschars on the body of scrub typhus patients: A prospective study. *Am J Trop Med Hyg* 76(5):806-9, 2007.)

Scrub typhus is frequently underdiagnosed as a cause of tropical fevers, often presenting as a fever of unknown origin and posing diagnostic difficulties similar to other rickettsial diseases. When it presents as encephalitis, it can be hard to distinguish from viral or bacterial causes of the condition. Its symptoms often overlap with flu-like illnesses, which can lead to misdiagnosis. Additionally, eschars, which appear in 50-80% of acute cases, are commonly missed.

Differential diagnoses to consider include malaria, dengue, leptospirosis, Q fever, typhoid, melioidosis, chikungunya fever and meningitis. The disease's ability to affect nearly every organ system further complicates diagnosis, resulting in delayed treatment.

In diagnosing and treating scrub typhus, healthcare professionals should maintain a high index of suspicion in appropriate epidemiological setting. base their decisions on clinical suspicion, followed by laboratory diagnosis. The lab diagnosis aids in confirming the diagnosis. This approach ensures that the appropriate measures are taken to manage the disease effectively and prevent potential complications. Lab finding may be suggestive of thrombocytopenia, elevation of hepatic enzymes, bilirubin, creatinine. There may be associated leukopenia or leukocytosis.

DIFFERENTIATING SCRUB TYPHUS ESCHAR FROM ANTHRAX ESCHAR

Understanding the difference between eschars caused by *Scrub Typhus* and *Anthrax* is essential for accurate diagnosis and appropriate treatment.

The table below provides a side-by-side comparison of both eschars. Observe the difference in appearance and note the distinctive features that can aid in diagnosis.

Feature	Scrub Typhus Eschar	Anthrax Eschar
Appearance	Shallow ulcer, resembles a cigarette burn, red edges	Nodular lesion with elevated margins, black scab
Common Locations	Axilla, groin, trunk, scrotal folds, sometimes scalp	Exposed areas like hands, arms, face, neck
Key Identifiers	Undermined edges, shallow ulcer	Elevated border, central black scab



Fig a: Scrub Typhus Eschar

a) <https://www.cdc.gov/typhus/scrub/index.html> ,



Fig b: Anthrax Eschar

b) <https://www.cdc.gov/vaccines/vpd/anthrax/photos.html>

Clinical Manifestations

- Fever (often accompanied by an eschar at the bite site), chills, severe headache, and generalized lymphadenopathy start suddenly; centrifugally spreading non confluent pink to red macular rash fades on pressure.
- If untreated, it leads to complications such as Interstitial Pneumonia, Meningoencephalitis, and Myocarditis.
- Important differential diagnosis for Scrub Typhus are Dengue, Malaria, and Typhoid.

Symptoms of Scrub Typhus



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SCRUB TYPHUS

Symptoms



• Clinical symptoms typically appear after an incubation period of 6-21 days (mean – 10 – 12 days).

• The development of an eschar, starting as a primary papular lesion and later forming a black ulcer with central necrosis, is a notable characteristic of scrub typhus, although its occurrence may vary by region.

• Treatment decision should be made based on clinical suspicion followed by laboratory diagnosis.

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SCRUB TYPHUS

Disease Progression

Acute onset with fever, chills, headache, and generalized lymphadenopathy

The eschar forms within a few days (median 5 days) after the bite.

Fever rises during the 1st week, often to 40 to 40.5° C

Macular rash develops on the trunk during the 5th to 8th day of fever, often extending to the arms and legs

Cough is present during the 1st week of fever, and pneumonitis may develop during the 2nd week.

In untreated patients, high fever may persist ≥ 2 weeks, then falls gradually over several days.



<https://www.cdc.gov/scrub-typhus-disease-in-malib-district-of-maldives/197742/>

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SCRUB TYPHUS

How to differentiate Anthrax Eschar from Scrub Typhus one?

Scrub Typhus Eschar	Anthrax Eschar
It resembles a cigarette burn type of shallow ulcer with undermined edges Commonly seen in axilla, groin, trunk, scrotal folds and rarely in scalp	It has a nodular lesion with elevated margins and black scab
	

<https://www.cdc.gov/scrub-typhus/>

<https://www.cdc.gov/evidence/guidelines/typhus.html>

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SCRUB TYPHUS

Notes

Differentiating Scrub Typhus Eschar from Anthrax Eschar

Feature	Scrub Typhus Eschar	Anthrax Eschar
Appearance	Shallow ulcer, resembles a cigarette burn, red edges	Nodular lesion with elevated margins, black scab
Common Locations	Axilla, groin, trunk, scrotal folds, sometimes scalp	Exposed areas like hands, arms, face, neck
Key Identifiers	Undermined edges, shallow ulcer	Elevated border, central black scab

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SCRUB TYPHUS

Notes

Session-4

Scrub Typhus in Animals

Course No. 004	Session 4: Scrub Typhus in Animals
Duration	15 minutes
Learning Objective	• Understand the disease transmission and clinical manifestation • Understand the differential diagnosis in animals
Pre-requisite knowledge/skill	• Basic knowledge of zoonotic disease transmission involving vectors and animal hosts. • Familiarity with clinical signs of febrile illnesses in domestic and wild animals. • Understanding of differential diagnosis methods for vector-borne infections in animals.
Competencies to be achieved	• Enumerate scrub typhus transmission in animals • Describing the clinical manifestation and differential diagnosis in animals

TYPHUS IN ANIMALS

Scrub Typhus is primarily known as a zoonotic disease, with rodents and small mammals serving as natural reservoir hosts for the causative bacterium, *Orientia tsutsugamushi*. While these animals typically do not exhibit the typical clinical symptoms seen in humans, it's important to acknowledge that they can still be affected by the infection. In animals, including rodents, common signs associated with scrub typhus infection may include fever, lethargy, anorexia, and various systemic manifestations. These signs can be subtle and challenging to detect in the wild animals, where animals often hide their illness as a survival instinct. In domestic animals, such as pets or livestock, caregivers and veterinarians may observe these clinical signs more easily.

Clinical Manifestations

Fever is a common manifestation of scrub typhus in infected animals, indicating an inflammatory response to the bacterium within their bodies. Lethargy and anorexia often accompany the fever, as the immune system works to combat the infection, sapping the animals' energy and appetite. Respiratory signs and muscular pain may also be observed, reflecting the systemic nature of the infection and the impact it has on various organ systems. Weight loss can occur as a consequence of reduced food intake due to anorexia and the energy expenditure associated with fighting the infection.

In addition to the aforementioned signs, scrub typhus in animals can lead to other clinical manifestations. Skin lesions may develop, although they may not be as pronounced as the eschar seen in humans. Ocular signs can also occur, affecting the eyes of infected animals. Enlarged lymph nodes may be palpable upon physical examination, as the lymphatic system responds to the infection. Behavioral changes, including irritability or altered activity patterns, can be observed as well. In severe cases, neurological signs may become apparent, further emphasizing the systemic nature of the disease. Reproductive issues and even abortions in pregnant animals have also been associated with scrub typhus.

While animals are often asymptomatic carriers of scrub typhus, these clinical signs and manifestations in infected animals highlight the need for continued research and surveillance to better understand the impact of this disease in both wildlife and domestic animals. Additionally, recognizing these signs in domestic animals is essential for timely diagnosis and treatment, as well as for preventing potential zoonotic transmission to humans in close contact with infected animals.



Lethargy



Enlarged lymph glands



Fig 11: Clinical signs in Animals

(Image source: <https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-019-4299-2>)

Differential Diagnosis

Different typhus types are associated with specific vectors and reservoir hosts, ranging from small mammals and rodents to humans and cattle. Understanding the differential diagnosis of typhus and rickettsial diseases is essential for effective disease management and prevention.

The table highlights various types of typhus, their vectors, reservoir hosts, modes of transmission, and incubation periods. Since these diseases share overlapping symptoms, distinguishing between them is crucial for accurate diagnosis and appropriate treatment. Identifying the specific vector and reservoir host helps in implementing targeted control measures, reducing the risk of transmission to humans and animals. Additionally, recognizing the incubation periods aids in early detection and timely intervention, minimizing the severity and spread of these infections.

Table 3: Differential Diagnosis of Scrub Typhus in Animals

Typhus Type	Vector	Reservoir Hosts	Transmission	Incubation Period
Rocky Mountain spotted fever	Ticks (e.g., <i>Dermacentor</i> spp.)	Various small mammals	Tick bites, primarily from infected tick	2-14 days
Epidemic typhus	Body lice (<i>Pediculus humanus</i>)	Humans	Louse feces contaminating skin breaks or inhalation of contaminated dust	6-14 days
Murine typhus	Fleas (mainly <i>Xenopsylla cheopis</i>)	Rats, mice, rodents	Flea bites, often from infected rodents	6-21 days
Scrub typhus	Chiggers (larval mites)	Small mammals, rodents	Mite bites	6-21 days
Rickettsial pox	Mites (<i>Liponyssoides sanguineus</i>)	Mice	Mite bites	7-14 days
African tick typhus	Ticks (mainly <i>Amblyomma</i> spp.)	Cattle, wild animals	Tick bites, primarily from infected ticks	5-7 days

Scrub Typhus has been reported in these animals:

Scrub Typhus has been reported in these animals:



Monkey



Rabbit



Guinea pig



Rat



Dogs & Cats



Pigeons



Hamster



Calves



Mice



Horse



Goats



Marsupials

Order for the Month: 10/20/2014

SCRUB TYPHUS



Lethargy



Enlarged lymph glands

Although animals are **asymptomatic carriers**, common signs in animals infected with Scrub Typhus include fever, lethargy, anorexia, respiratory signs, muscular pain, weight loss, skin lesions, ocular signs, enlarged lymph nodes, behavioral changes, neurological signs, reproductive issues, abortions.

<https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-019-4290-2>

Center for the Study of Health, NCHC, Montreal

SCRUB TYPHUS

Transmission Type	Vector	Reservoir Hosts	Target
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Typhus Type	Vector	Reservoir Hosts	Transmission	Incubation Period
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Murine typhus	Fleas (mainly Xenopsylla cheopis)	Rats, mice, rodents	Flea bites, often from infected rodents	6-21 days
Scrub typhus	Chiggers (larval mites)	Small mammals, rodents	Mite bites	6-21 days
Rickettsial pox	Mites (Liponyssoides sanguineus)	Mice	Mite bites	7-14 days
African tick typhus	Ticks (mainly Amblyomma spp.)	Cattle, wild animals	Tick bites, primarily from infected ticks	5-7 days

Center for New Health, NCHC, Beijing

SCRUB TYPHUS

[illegible]

Session-5

Diagnosis of Scrub Typhus

Course No. 005	Session 5: Diagnosis of Scrub Typhus
Duration	30 minutes
Learning Objectives	• Understanding the case definition and differential diagnosis • Understand the diagnostic algorithm and different technologies required for scrub typhus laboratory diagnosis • A case scenario to understand the diagnosis
Pre-requisite knowledge/skill	• Basic understanding of clinical case definitions and diagnostic criteria. • Familiarity with laboratory techniques such as serology and molecular diagnostics. • Knowledge of diagnostic algorithms used for identifying rickettsial infections.
Competencies to be achieved	• Demonstrate different modalities of laboratory diagnosis of Scrub Typhus. • Basics of different technologies (serology, molecular biology, culture, etc.) used for Scrub Typhus diagnosis.

CASE DEFINITION

The case definition for scrub typhus in humans is a crucial tool for healthcare professionals, epidemiologists, and researchers to identify and classify individuals with the disease. It helps ensure that accurate diagnoses are made and that cases are appropriately managed. Scrub typhus presents with a range of clinical symptoms, making a well-defined case definition essential for diagnosis and surveillance.

Suspected/clinical case: Acute undifferentiated febrile illness of five days or more with or without eschar should be suspected as a case of rickettsial infection (if eschar is present, fever of less than five days duration should also be considered as scrub typhus). Other presenting features may be headache and rash (rash more often seen in fair persons), after encephalopathy lymphadenopathy, multi-organ involvement like liver, lung and kidney and acute respiratory distress. Patients presenting with features of AES could be scrub typhus.

The differential diagnosis of dengue, malaria, pneumonia, leptospirosis and typhoid should be kept in mind.

Probable case: A suspected clinical case showing significant titers (1:80 or above) in OX2, OX19 and OXK antigens by Weil-Felix test and an optical density (> 0.5 or evaluated with locally determined cutoff) for IgM antibodies by specific group ELISA is considered positive.

Confirmed case: A case compatible with the clinical description of scrub typhus with at least one of the following:

1. High titre of IgM antibodies in ELISA (evaluated with locally determined cutoff) for single clinical sample*.
2. A four-fold rise in the Weil-Felix test (total antibodies) between acute and convalescent-phase serum specimens run in parallel.
3. Seroconversion on ELISA/ IFAT (demonstrating the conversion of IgM to IgG antibodies).

*A single serum sample showing high titres of IgM antibodies may indicate acute infection. These 1-3 tests are the preferred tests as ELISA are widely acceptable.

Other: Isolation and Validated PCR can be done in patients who have not received antibiotic and in early stage of diseases (preferably less than 7 days)

DIFFERENTIAL DIAGNOSIS OF SCRUB TYPHUS

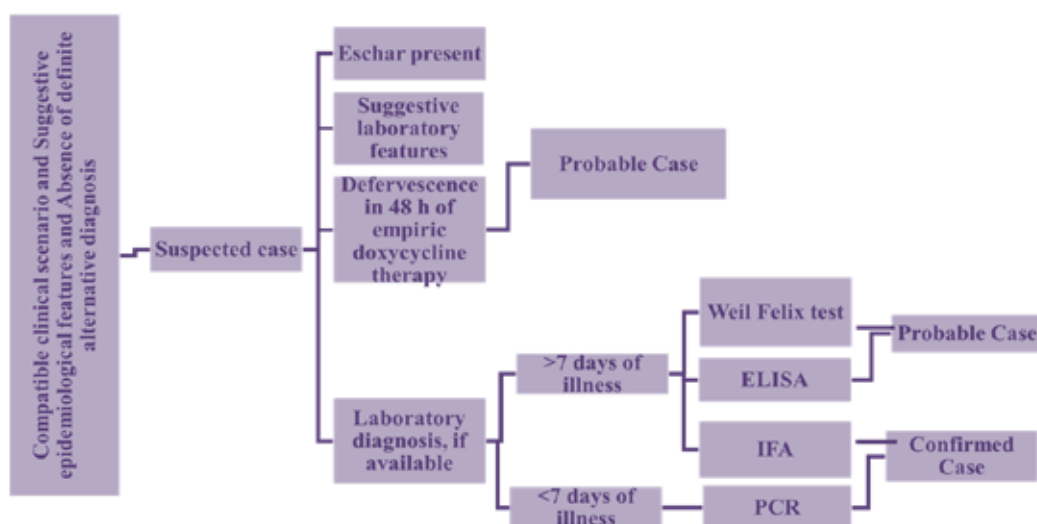
Differential diagnosis is crucial to avoid misdiagnosis and to initiate appropriate treatment.

Table 4: *Differential Diagnosis of Scrub Typhus*

The following conditions should be considered in the differential diagnosis of scrub typhus:

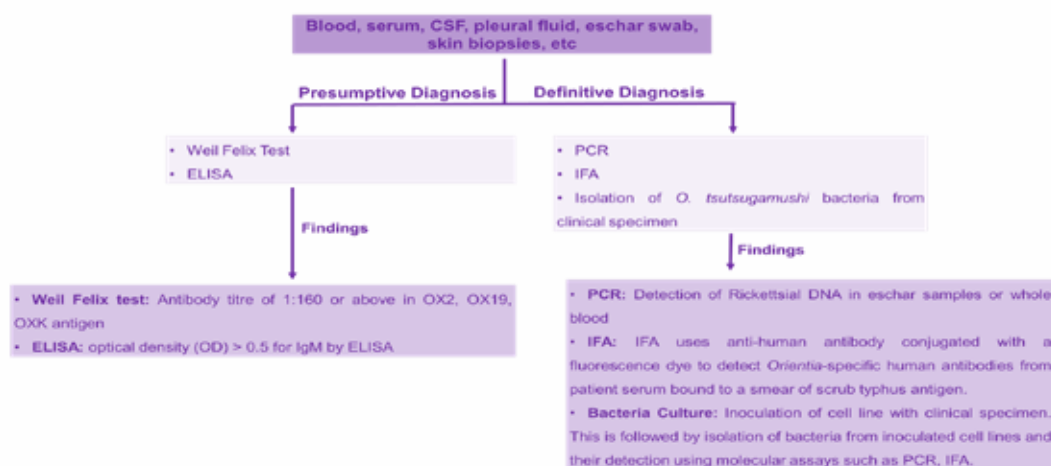
Disease	Epidemiological Clues	Key Clinical Differences	Laboratory Differences	Biochemical Tests & Elevated Markers
Typhoid Fever	Endemic areas, exposure to contaminated food or water	Stepwise fever, abdominal pain, relative bradycardia	Blood culture, Widal test	Widal test, Elevated CRP, ESR
Dengue Fever	Endemic areas, recent travel to affected regions	Severe muscle pain, retro-orbital pain, distinct rash	Serological tests for dengue virus	Elevated ALT, AST in Liver Function Tests
Leptospirosis	Water contamination, occupational exposure	Jaundice, conjunctival suffusion, renal involvement	Serological tests, urine culture	Elevated creatinine, BUN in RFT; Elevated ALT, AST in LFT
Malaria	Endemic areas, recent travel to malaria regions	Cyclic fever, anemia, splenomegaly	Blood smear, rapid diagnostic tests	Anemia, thrombocytopenia in CBC
Other Rickettsial Infections	Specific endemic areas for rickettsial diseases	Similar rash and eschar patterns	Serological tests for rickettsial species	Elevated inflammatory markers (CRP, ESR) (not specific)
Viral Hemorrhagic Fevers	Endemic areas, recent travel to affected regions	Hemorrhagic symptoms, severe systemic illness	Serological tests for specific viruses	Prolonged PT, aPTT in coagulation studies
Sepsis and Bacterial Infections	Underlying conditions, invasive procedures	Rapid onset, multiorgan dysfunction, lack of eschar	Blood cultures, inflammatory markers	Leukocytosis/Leukopenia, Elevated CRP, ESR, Procalcitonin
Brucellosis	Occupational exposure, unpasteurized dairy consumption	Undulant fever, arthralgia, fatigue, animal contact	Serological tests for Brucella spp.	Elevated ALT, AST in LFT, CBC abnormalities
Tuberculosis	Exposure to TB cases, immunocompromised states	Chronic fever, weight loss, night sweats, pulmonary symptoms	Chest X-ray, sputum culture, tuberculin skin test	Tuberculin skin test, IGRA (Interferon-gamma release assay)
Japanese Encephalitis	Endemic areas, recent travel	Neurologic symptoms, altered mental status	CSF analysis, serological tests	CSF abnormalities (e.g., elevated protein, lymphocytic pleocytosis)

Diagnostic & Clinical Algorithm for Scrub Typhus Infection



LABORATORY DIAGNOSIS

Laboratory diagnosis for scrub typhus is crucial for accurately identifying and confirming cases of this infectious disease. There are two main approaches to diagnosing scrub typhus in a clinical laboratory setting: direct and indirect methods.



Sampling Window

"Sampling Window" provides a comprehensive guide on the optimal timing for diagnostic testing in scrub typhus. It outlines three distinct phases of the disease: acute, transition, and chronic/recovery.

During the acute phase (days 1-7), blood culture and RT-PCR are recommended for early detection of the *Orientia tsutsugamushi* DNA.

As the disease progresses to **the transition phase (days 7-14),** IgM ELISA becomes the preferred test to detect recent infection.

In the **chronic/recovery phase (days 14-21)**, IgG ELISA is used to confirm past infection. Additionally, coagulation profile and chest X-ray may be necessary to assess for potential complications like disseminated intravascular coagulation (DIC) and respiratory involvement. By following this sampling window, healthcare providers can accurately diagnose scrub typhus and initiate timely treatment.

Table 5: Sampling window

Time Frame	Symptoms	Sample	Diagnostic Tests
Day 1-7	Fever, headache, myalgia, fatigue, anorexia	Blood (Serum/ Plasma)	Blood culture (gold standard for early detection)
			RT-PCR (Detects Orientia tsutsugamushi DNA)
Day 7-14 (Transition Phase)	Persistent fever, localized pain (arthralgia, back pain)	Blood (Serum/ Plasma)	IgM ELISA (Detects recent infection)
			Weil-Felix test (Cross-reactivity with other rickettsial infections)
Day 14-21 (Chronic/ Recovery Phase)	Resolving or recurrent symptoms, complications like pneumonia or myocarditis	Blood (Serum/ Plasma)	IgG ELISA (Indicates ongoing or past infection)
			Coagulation Profile (for DIC)
			Chest X-ray (for respiratory complications)

Table 6: Supportive Laboratory Investigations

Category	Description
Haematology	Total Leucocytes Count: During the early course of the disease, the count may be normal, but later it may become elevated to more than 11,000/cu. mm. Thrombocytopenia: Majority of patients with scrub typhus show thrombocytopenia, with platelet count less than 100,000/cu. mm.
Biochemistry	Raised Transaminase Levels: Commonly observed in patients with scrub typhus. Elevated levels of transaminases indicate liver involvement and can serve as an additional diagnostic clue.

Direct Laboratory Diagnosis

- A. PCR (Polymerase Chain Reaction):** This direct method involves detecting the genetic material of the *Orientia tsutsugamushi* bacterium in patient samples, such as eschar tissue or whole blood. PCR is a highly sensitive and specific technique that allows for rapid and precise diagnosis. It's particularly useful in the early stages of the disease when antibody responses may not have developed fully.
- B. Culture:** Direct methods of diagnosis involve bacterial isolation and culturing in chick embryos or established cell lines such as L929, Vero, BHK, McCoy and HeLa cells and their detection using molecular assays such as ELISA and PCR. Culture of *O. tsutsugamushi* require biosafety level (BSL) 3 facilities and therefore, this test is limited to medical colleges and research lab.

Indirect Laboratory Diagnosis

- A. Weil-Felix Test:** Weil Felix test is a serological Assay that is used for the diagnosis of rickettsial infection by indicating immunoglobulins/antibodies in the serum. This test is a nonspecific agglutination test that utilizes antigenic cross-reactivity between rickettsiae and certain non-motile proteus serotypes for detection of anti-rickettsial antibodies (so-called Weil-Felix antibodies) in a patient's serum. Both rickettsial antigen and Proteus OX (O-specific polysaccharide chain of outer membrane lipopolysaccharide) antigens are recognized by anti-rickettsial antibodies in a patient's serum; upon mixing serum that contains anti-rickettsial antibodies with OX antigen, the resulting reaction can indicate previous or current rickettsial infection. The rickettsial target of these antibodies was determined to be the lipopolysaccharide (LPS) O-antigen, which is highly conserved across the rickettsiae groups.
- B. ELISA (Enzyme-Linked Immunosorbent Assay):** ELISA techniques, particularly immunoglobulin M (IgM) capture assays for serum, is a sensitive test available for rickettsial diagnosis and the presence of IgM antibodies, indicate comparatively recent infection with rickettsial disease.
National essential diagnostic list published by ICMR recommends serum collection and its transportation to District hospital for ELISA.
- C. Immunofluorescence Assay (IFA):** IFA is a highly sensitive and specific serological method used to detect antibodies against *Orientia tsutsugamushi*. It uses fluorescein linked anti-human reporter antibody to detect the presence of scrub typhus-specific antibodies in the serum sample.

Baseline titers and ELISA cutoffs for the Weil-Felix test, Enzyme-Linked Immunosorbent Assay (ELISA), and Indirect Immunofluorescence (IIF) should be standardized for each region.

Table 7: Advantages and Disadvantages of Available Direct and Indirect Diagnostic Technologies

Method	Merits	Demerits
Polymerase Chain Reaction (PCR)	• Higher sensitivity and specificity	• Higher genetic diversity among <i>O. tsutsugamushi</i> serotypes
	• Short response time	• Higher DNA recovery from eschar than blood samples
	• Higher accuracy	• False negatives in patients with prior antibiotic treatment
		• Unavailability in remote areas
		• Requires an expert to perform
Cell Culturing	• Improves sensitivity by bacterial propagation in low-concentration samples	• Requires BSL-3 facility
	• Hemoculture can be used as a transport tool for remote areas	• Slow growth rate (takes at least 2 days)
		• Requires an expert to handle cell lines
ICT (Immunofluorescence Assay)	• Point-of-care diagnosis	• Higher antigenic diversity among serotypes
	• Does not require sophisticated instruments	• Less sensitive and specific than other gold-standard tests
	• Cheaper in cost	
	• Suitable for remote areas	
IFA (Immunofluorescence Assay)	• Higher sensitivity and specificity	• Requires paired sampling
	• Higher accuracy	• Higher antigenic diversity among serotypes
	• Gold standard test for scrub typhus	• No accurate antibody titer cutoff value
		• Requires sophisticated instruments
Weil-Felix Test	• Easy to perform	• Lower specificity
	• Rapid response time	• Cross-reactivity
	• Cheaper in cost	• Unreliable results
ELISA (Enzyme-Linked Immunosorbent Assay)	• Higher sensitivity and specificity	• Requires paired sampling
	• Higher accuracy	• Higher antigenic diversity among serotypes
	• Easy to perform	• No specified antibody titer cutoff value
	• Does not require sophisticated instruments	

CASE SCENARIO

Case Study: Scrub Typhus Presenting with Fever and Altered Consciousness

Patient Profile:

- **Age/Sex:** 53-year-old male
- **Presenting Complaints:** Fever, headache, vomiting, and altered consciousness for the last two days
- **Informant:** Son (fair reliability)
- **Past Medical History:** Known hypertensive on regular medication
- **Social History:** Teetotaler, nonsmoker

Clinical Presentation:

The patient initially experienced a low-grade fever that progressed to a high-grade fever, associated with chills and rigors. Confusion and disorientation developed two days before hospitalization. There was no history of seizures, cough, or dysuria.

On examination:

- **General Condition:** Febrile and disoriented to time, place, and person
- **Vital Signs:** BP - 170/100 mmHg
- **CNS Examination:** No meningeal signs, no cranial nerve deficits except for bilateral papilledema
- **Skin Examination:** A brownish-black-crust lesion (eschar) with surrounding erythema was found below the left axilla
- **Other Systemic Examination:** Unremarkable

Investigations:

- **Hematology:**
 - ◇ TLC: 14,230/cmm (85% polymorphs)
 - ◇ Hemoglobin and platelets: Normal
- **Liver Function Tests:**
 - ◇ ALT: 99 U/L, AST: 122 U/L
 - ◇ GGT: 300 U/L, ALP: 304 U/L
- **Imaging & Other Tests:**
 - ◇ **USG Abdomen:** Mild hepatosplenomegaly
 - ◇ **Chest X-ray:** Normal
 - ◇ **NCCT Head:** Features of early cerebral edema
- **Cerebrospinal Fluid (CSF) Analysis:**
 - ◇ Glucose: 45 mg/dL, Protein: 78 mg/dL
 - ◇ Cells: 202/ccm (lymphocytic predominance)
 - ◇ AFB negative, ADA: 5 U/L
 - ◇ GeneXpert, viral antibodies (HSV, JE) negative

- **Leptospira RDT:** Negative
- **IgM Scrub Typhus (Day 2 of hospitalization):** 1.25 (Normal range <0.14)

Diagnosis:

Scrub Typhus with CNS Involvement

Discussion:

Scrub typhus, caused by *Orientia tsutsugamushi* and transmitted by chigger mite bites, is an endemic rickettsial disease with varied clinical presentations. The hallmark clinical feature is an **eschar**, a punched-out ulcer covered with a blackened scab, resembling a cigarette burn, seen at the chigger bite site. The disease typically presents with **high fever (104°-105°F)**, **headache**, **malaise**, **lymphadenopathy**, and **lymphocytosis**. Around the fifth day of illness, some patients may develop a **macular rash**.



Eschar seen below right nipple



Eschar seen in left flank



Erythematous Papule on right arm capped by a well-defined Blackish Scab

Fig 12: Bite mark 'eschar' is a pathognomonic clinical feature of scrub typhus that occurs at the site of the chigger feeding. It appears as an ulcer that enlarges and undergoes central necrosis to finally turn into a black crust. This particular skin lesion may appear similar to a skin burn from a cigarette.

In this case, the presence of **fever**, **altered sensorium**, **hepatosplenomegaly**, **transaminitis**, **lymphocytic pleocytosis in CSF**, and a **positive IgM for scrub typhus** strongly suggests **scrub typhus** with CNS involvement. The finding of **early cerebral edema** on NCCT further supports the severity of the infection.

Conclusion:

Early recognition and prompt initiation of **doxycycline** or **azithromycin** are crucial in scrub typhus management. Left untreated, complications such as **meningoencephalitis**, **multi-organ dysfunction**, or **acute respiratory distress syndrome (ARDS)** can develop. This case highlights the importance of considering scrub typhus in febrile patients presenting with neurological symptoms, especially in endemic regions. The presence of an **eschar** is a critical diagnostic clue that should not be overlooked.

Case Classification (Humans)

Suspected

Acute undifferentiated febrile illness of five days or more with or without eschar should be suspected as a case of rickettsial infection. (if eschar is present, fever of less than five days duration should be considered as scrub typhus).
Other presenting features may be headache and rash (rash more often seen in fair persons), lymphadenopathy, multi-organ involvement like liver, lung and kidney and acute respiratory distress.

Probable

A suspected clinical case showing titres of 1:80 or above in OX2, OX19 and OXK antigens by **Weil-Felix test**.
Optical Density (OD) > 0.5 for IgM by ELISA is considered positive for members of typhus and spotted fever groups of Rickettsiae.

Confirmed

A case compatible with the clinical description of scrub typhus with at least one of the following:
• **High titre of IgM antibodies in ELISA** (evaluated with locally determined cutoff) for single clinical sample".
• **A four-fold rise in the Weil-Felix test** (total antibodies) between acute and convalescent-phase serum specimens run in parallel.
• **Seroconversion on ELISA/IFAT** (demonstrating the conversion of IgM to IgG antibodies).

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SCRUB TYPHUS

Differential Diagnosis

Disease	Key Clinical Differences	Laboratory Differences	Epidemiological Clues	Biochemical Tests & Elevated Markers
Typhoid Fever	Stepwise fever, abdominal pain, relative bradycardia	Blood culture, Widal test	Endemic areas, exposure to contaminated food or water	Widal test, Elevated CRP, ESR
Dengue Fever	Severe muscle pain, retro-orbital pain, distinct rash	Serological tests for dengue virus	Endemic areas, recent travel to affected regions	Elevated ALT, AST in Liver Function Tests
Leptospirosis	Jaundice, conjunctival suffusion, renal involvement	Serological tests, urine culture	Water contamination, occupational exposure	Elevated creatinine, BUN in RFT; Elevated ALT, AST in LFT
Malaria	Cyclic fever, anemia, splenomegaly	Blood smear, rapid diagnostic tests	Endemic areas, recent travel to malaria regions	Anemia, thrombocytopenia in CBC
Other Rickettsial Infections	Similar rash and eschar patterns	Serological tests for rickettsial species	Specific endemic areas for rickettsial diseases	Elevated inflammatory markers (CRP, ESR) (not specific)
Viral Hemorrhagic Fevers	Hemorrhagic symptoms, severe systemic illness	Serological tests for specific viruses	Endemic areas, recent travel to affected regions	Prolonged PT, aPTT in coagulation studies
Sepsis and Bacterial Infections	Rapid onset, multiorgan dysfunction, lack of eschar	Blood cultures, inflammatory markers	Underlying conditions, invasive procedures	Leukocytosis/Leukopenia, Elevated CRP, ESR, Procalcitonin
Brucellosis	Undulant fever, arthralgia, fatigue, animal contact	Serological tests for Brucella spp.	Occupational exposure, unpasteurized dairy consumption	Elevated ALT, AST in LFT, CBC abnormalities
Tuberculosis	Chronic fever, weight loss, night sweats, pulmonary symptoms	Chest X-ray, sputum culture, tuberculin skin test	Exposure to TB cases, immunocompromised states	Tuberculin skin test, IGRA (Interferon-gamma release assay)
Japanese Encephalitis	Neurologic symptoms, altered mental status	CSF analysis, serological tests	Endemic areas, recent travel	CSF abnormalities (e.g., elevated protein, lymphocytic pleocytosis)

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SCRUB TYPHUS

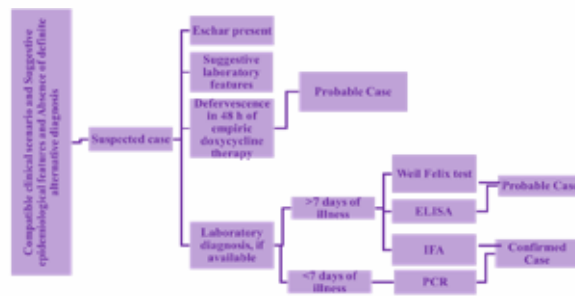
Differential Diagnosis Of Rickettsial Diseases (Humans)

Disease	Rash Characteristics	Distribution of Rash	Additional Symptoms and Complications
Indian Tick typhus	Maculopapular (small, red, flat, or raised spots) and may become petechial	Palms and soles, and may spread to the trunk.	Hepatomegaly, splenomegaly, and, in severe cases, encephalitis or multi-organ involvement.
Epidemic typhus	Axillary folds, trunk, peripheral spread	Rarely involves palms, soles, face	Physiological and pathological abnormalities similar to RMSF
Murine typhus	Non-purpuric, non-confluent, less extensive	-	Uncommon renal and vascular complications
Scrub typhus	Similar to RMSF and epidemic typhus, eschar common	Different geographic areas	Eschar development with satellite adenopathy
Rickettsial pox	Vesicles with surrounding erythema	Sparse rash, resembling varicella	Mild disease presentation

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SCRUB TYPHUS

Diagnostic & Clinical Algorithm for Scrub Typhus Infection



Note: Baseline titers and ELISA cutoffs for the Weil-Felix test, ELISA, and IFA should be standardized for each region.

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SCRUB TYPHUS

Notes

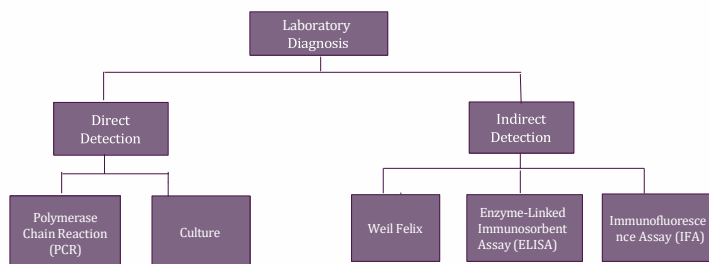
Sampling Window

Time Frame	Symptoms	Sample	Diagnostic Tests
Day 1-7 (Acute Phase)	- Fever, headache, myalgia, fatigue, anorexia	Blood (Serum/Plasma)	- Blood culture (gold standard for early detection) - RT-PCR (Detects <i>Orientia tsutsugamushi</i> DNA) - IgM ELISA (Detects recent infection)
Day 7-14 (Transition Phase)	- Persistent fever, localized pain (arthralgia, back pain)	Blood (Serum/Plasma)	- Weil-Felix test (Cross-reactivity with other rickettsial infections) - IgG ELISA (Indicates ongoing or past infection)
Day 14-21 (Chronic/Recovery Phase)	- Resolving or recurrent symptoms, complications like pneumonia or myocarditis	Blood (Serum/Plasma)	- Coagulation Profile (for DIC) - Chest X-ray (for respiratory complications)

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SCRUB TYPHUS

Laboratory Diagnosis



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SCRUB TYPHUS

Laboratory Tests

Diagnostic Method	Description
Weil-Felix Testing	An older test with low sensitivity and specificity for scrub typhus diagnosis.
Indirect Immunofluorescence Antibody (IFA)	Considered the gold standard, but requires repeat testing and is retrospective, limiting its usefulness for initial management.
Indirect Immunoperoxidase (IIP)	Modified version of IFA, provides similar results without the need for a fluorescent microscope.
Enzyme-linked Immunoabsorbent Assays (ELISA)	Preferred method for acute scrub typhus diagnosis, using specific antigens and IgM antibodies for detection.
Polymerase Chain Reaction (PCR)	Highly sensitive, detects infection before antibodies are detectable, but cost and antibiotic interference are concerns.
Bacterial Culture	Challenging process due to the nature of the pathogen, mainly used for research purposes in reference laboratories.
Cerebrospinal Fluid (CSF) Evaluation	Helpful for patients with signs of central nervous system involvement, with lymphocytic pleocytosis observed in scrub meningitis.
Chest Radiographs	Obtained for patients with respiratory symptoms, can reveal pleural effusions, pneumonia, and acute respiratory distress syndrome (ARDS).

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SCRUB TYPHUS

Supportive Laboratory Investigations

Category	Description
Haematology	Total Leucocytes Count: During the early course of the disease, the count may be normal, but later it may become elevated to more than 11,000/cu. mm. Thrombocytopenia: Majority of patients with scrub typhus show thrombocytopenia, with platelet count less than 100,000/cu. mm.
Biochemistry	Raised Transaminase Levels: Commonly observed in patients with scrub typhus. Elevated levels of transaminases indicate liver involvement and can serve as an additional diagnostic clue.

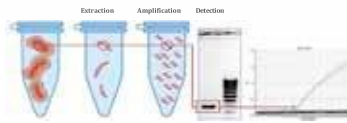
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SCRUB TYPHUS

Notes

Polymerase Chain Reaction (PCR)

- National Centre for disease control (NCDC), India recommends PCR as diagnostic tool for detection of scrub typhus. It is a rapid and specific test for diagnosis.
- It can be used to detect scrub typhus DNA in whole blood and eschar samples.
- The results are best within first week for blood sample because of presence of rickettsia (*O. tsutsugamushi*) in first 7-10 days.
- Real-time PCR kit is intended for detection of *O. tsutsugamushi* microorganism. The primers are designed against Scrub typhus specific antigens such as Membrane Protease (htrA) gene, 56 kDa TSA gene, etc.



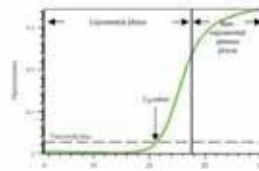
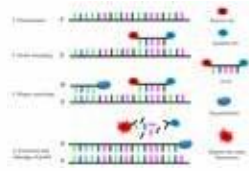
Source: *Microbiology: Preparation and response, OpenWang*

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SCRUB TYPHUS

Procedure for Real Time PCR

- Kit contains a specific ready-to-use system for the detection of the *O. tsutsugamushi* using the real-time PCR system
- Fluorescence is emitted and measured by the real time systems' optical unit during the PCR.
- In real-time PCR, the accumulation of amplification product is measured as the reaction progresses, in real time, with product quantification after each cycle.



Source: *Microbiology and Molecular Diagnostics in Pathology, 2017*

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SCRUB TYPHUS

Culture

Direct methods of diagnosis involve bacterial isolation and culturing in chick embryos or established cell lines such as L929, Vero, BHK, McCoy and HeLa cells and their detection using molecular assays such as ELISA and PCR

Culture of *O. tsutsugamushi* require biosafety level (BSL) 3 facilities and therefore, this test is limited to medical colleges and research lab.

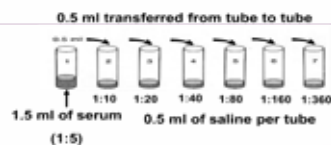
- Collect up to 5 ml of blood into EDTA tubes from patients with suspected rickettsiosis.
- Whole EDTA-anticoagulated blood (1 ml) is mixed with 5 ml of RPMI 1640 medium supplemented with 10% fetal calf serum and is used as an inoculum.
- Inoculation is performed directly in 12.5-cm² flasks containing irradiated L929 or Vero cell monolayers at 80% confluence
- The inoculated cells are incubated over shaker for 1 hour at room temperature, then the supernatant is replaced with fresh medium before incubation in a CO₂ incubator at 37°C.
- Ten days after inoculation, the culture is harvested by gently shaking 5-mm sterile glass beads over the cells.
- The cell suspension is pelleted by centrifugation at 8,000 rpm for 30 minutes at 4°C
- The pellets is then resuspended in sucrose renografin magnesium chloride (SRM) solution
- To ensure stability of isolates, *O. tsutsugamushi*-infected cells is repeatedly passaged onto fresh irradiated L-929 cells until heavy infection is observed.
- Giemsa staining, Immunofluorescence Assay (IFA) with *O. tsutsugamushi* hyperimmune serum, and PCR are used to identify *O. tsutsugamushi* in cell culture.

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SCRUB TYPHUS

Weil-Felix Test

- Weil Felix test is a serological Assay that is used for the diagnosis of rickettsial infection by indicating immunoglobulins/antibodies in the serum.
- This test is a nonspecific agglutination test that utilizes antigenic cross-reactivity between rickettsiae and certain non motile *Proteus* serotypes for detection of anti-rickettsial antibodies (so-called Weil-Felix antibodies) in a patient's serum.
- Both rickettsial antigen and *Proteus* OX (O-specific polysaccharide chain of outer membrane lipopolysaccharide) antigens are recognized by anti-rickettsial antibodies in a patient's serum; upon mixing serum that contains anti-rickettsial antibodies with OX antigen, the resulting reaction can indicate previous or current rickettsial infection.
- The rickettsial target of these antibodies was determined to be the lipopolysaccharide (LPS) O-antigen, which is highly conserved across the rickettsiae groups.



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SCRUB TYPHUS

Notes

It is a technique that uses a two-step process for detection, whereby a primary antibody specific for the antigen binds to the target, and a labeled secondary antibody against the host species of the primary antibody binds to the primary antibody for detection.

National essential diagnostic list published by ICMR recommends serum collection and its transportation to District hospital for ELISA.

Indirect ELISA
Source: Lector Technologies, Inc.

Order for the Month: 10/20/2019

SCRUB TYPHUS

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graph TD
    SAMPLE[SAMPLE] --> SERUM[SERUM]
    SERUM --> ELISA_PLATE[ELISA PLATE]
    ELISA_PLATE --> ELISA_WASHER[ELISA WASHER]
    ELISA_WASHER --> ELISA_REAGENTS_2[ELISA REAGENTS]
    ELISA_REAGENTS_2 --> INCUBATION[INCUBATION]
    INCUBATION --> ELISA_READER[ELISA READER]
    ELISA_READER --> READING[READING OF OD VALUES]
    READING --> ELISA_PLATE
  
```

Center for Drug Research, NCI/NCJ, Bethesda

SCRUB TYPHUS

Indirect

Fluorophore

Secondary antibody (anti-antibody)

Primary antibody

Antigen

Source: Science Photo Library

Order for the Month: 10/20/2016

SCRUB TYPHUS

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graph TD
    Title[Direct Methods of Diagnosis  
(Scrub Typhus)]
    Title --> PCR
    Title --> CellCult[Cell culturing]
    PCR <--> CellCult
  
```

Direct Methods of Diagnosis (Scrub Typhus)

Method	Merita	Demerita
Polymerase Chain Reaction (PCR)	- Higher Sensitivity and specificity - Short Response time - Higher accuracy	- Higher genetic diversity among serotypes of <i>Orientia tsutsugamushi</i> - Higher recovery of DNA from eschar samples as compare to blood samples - False negative results in patients having prior antibiotic treatment - Unavailability of technique in remote areas - Need expertise person to perform
Cell culturing	- Improve sensitivity of diagnosis method by propagation of bacterial cells to increase sample density where bacterial concentration is lower - Homoculture can act as a simple transport tool for samples from remote areas	- Requires BSL-3 for cell culturing - Slow growth rate takes at least 2 days to grow in cell lines - Need expertise person to handle cell lines

Source: Diagnosis of scrub typhus: recent advancements and challenges *Biotech* (2020) 10:396 <https://doi.org/10.1007/s13205-020-02989-z> Received: 26 May 2020 / Accepted: 10 August 2020 / Published online: 18 August 2020 © King Abdulaziz City for Science and Technology 2020

Center for Drug Research, NIDDK, NIH

SCRIB. TYPHUS

[illegible]

Advantages and Disadvantages of Available Diagnostic Technologies continued.....



Source: Diagnosis of scrub typhus: recent advancements and challenges J Biotech (2020) 10:394 <https://doi.org/10.1007/s10265-020-01202-z> Received: 24 May 2020 / Accepted: 10 August 2020 / Published online: 10 August 2020 © King Abdulaziz City for Science and Technology 2020

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SCRUB TYPHUS



Patient Information

A 53-year-old male presented to the Emergency Department Institute with **fever, headache, vomiting, and altered consciousness** for the last 2 days. The informant was his son with fair reliability. The fever was initially low grade but had become high grade and was associated with **chills and rigors**. He developed **confusion and disorientation** a day 2 days before hospitalization. There was **no history of seizures, cough, or dysuria**. He was **known hypertensive** and on regular medications. He was a **teetotaler and nonsmoker**. On examination, the patient was **disoriented to time, place, and person, was febrile, and had a blood pressure (BP) record of 170/100 mmHg**. He **did not have any icterus, rashes, or signs of meningeal irritation**. Cranial nerve examination revealed **no deficit except bilateral papilledema**. Other systemic examinations were normal. On further careful examination, you find that there is a **brownish-black-crusted lesion** with surrounding erythema-eschar was found below the left axilla.

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Investigation



- Investigations revealed **normal urine routine examination**. CBC revealed **TLC of 14,230/cmm polymorph 85%, with normal Hb and platelets**.
- The **liver function tests** revealed **transaminitis and cholestasis (ALT 99U/L, AST 122U/L, Gamma-glutamyl transferase (GGT) 300 U/L, and alkaline phosphatase of 304 U/L)**. USG of the abdomen revealed **mild hepatosplenomegaly**.
- Chest X-ray view was **normal**.
- Leptospira **Rapid Diagnostic Test (RDT)** was **negative**.
- A **non-contrast computed tomography scan of the head** revealed features of **early cerebral edema**.
- Cerebrospinal fluid (CSF)** studies revealed **glucose of 45 mg/dL, protein of 78 mg/dL, cells of 202/ccm with lymphocytic predominance, negative for acid-fast bacilli, and adenosine deaminase of 5 U/L, and GeneXpert was negative**.
- CSF viral antibodies for Herpes simplex virus and Japanese encephalitis were negative**. **IgM for the scrub typhus on day 2 of hospitalization was 1.25 (normal range <0.14)**.

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Symptoms

Typical

- ⓈThe disease onset is **abrupt** and characterized by symptoms such as **chills, high fever (104°-105°F), headache, malaise, and prostration**.
- ⓈAround the 5th day of illness, a **macular rash** develops.
- Ⓢ**Generalized lymphadenopathy** (enlarged lymph nodes) and **lymphocytosis** (increased lymphocyte count) are commonly observed.

Unique

- ⓈA notable characteristic is the presence of a **punched-out ulcer** covered with a **blackened scab**, known as an **eschar**, indicating the **site of the mite bite**.

Diagnosis

Scrub Typhus with CNS Involvement

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SCRUB TYPHUS

Notes

Clinical Signs

The bite mark '**eschar**' is a pathognomonic clinical feature of scrub typhus that occurs at the site of the chigger feeding. It appears as an ulcer that enlarges and undergoes central necrosis to finally turn into a black crust. This particular skin lesion may appear similar to a skin burn from a cigarette.



Eschar seen below right nipple



Eschar seen in left flank



Erythematous Papule on right arm capped by a well-defined Blackish Scab

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SCRIBE TYPHUS

Disease Progression

- Acute onset with fever, chills, headache, and generalized lymphadenopathy being usually present
- The eschar forms within a few days (median 5 days) after the bite.

Fever rises during the 1st week, often to 40 to 40.5° C

In untreated patients, high fever may persist ≥ 2 weeks, then falls gradually over several days.

- Cough is present during the 1st week of fever, and pneumonitis may develop during the 2nd week.
- Macular rash develops on the trunk during the 5th to 8th day of fever, often extending to the arms and legs



The first sign of scrub typhus disease in patients is a vesicular lesion at the site of mite feeding, which later on becomes an eschar or an ulcer with regional lymphadenopathy.

Center for Drug Abuse, NIDA, NIH

SCRUB TYPHUS

Discussion

- **Scrub typhus** is caused by *Orientia tsutsugamushi* and transmitted by chigger mite bites.

- It is an **endemic rickettsial disease** with varied clinical presentations.
- **Hallmark clinical feature:** Presence of an **eschar**, a punched-out ulcer covered with a blackened scab, resembling a **cigarette burn**, seen at the chigger bite site.

- Common clinical symptoms

- High fever (104°-105°F)
- Headache
- Malaise
- Lymphadenopathy
- Lymphocytosis
- Around the **fifth day of illness**, some patients may develop a **macular rash**.

- Case findings suggestive of scrub typhus with CNS involvement

- Fever and **altered sensorium**
- **Hepatosplenomegaly**
- **Transaminitis**
- **Lymphocytic pleocytosis** in CSF
- **Positive IgM** for scrub typhus
- **Early cerebral edema** seen on NCCT, indicating severity of infection.

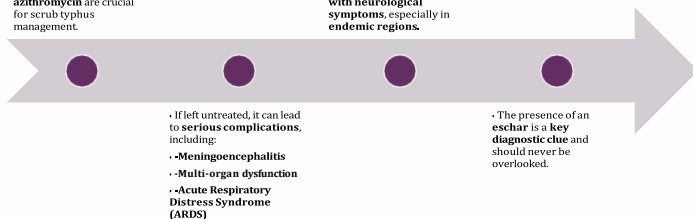
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SCRUB TYPHUS

Conclusion

- Early recognition and prompt treatment with doxycycline or azithromycin are crucial for scrub typhus management.

- This case highlights the need to **consider scrub typhus** in febrile patients with neurological symptoms, especially in endemic regions.



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SCRUB TYPHUS

Notes

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Session-6

Prevention & Treatment

Course No. 006	Session 6: Prevention & Treatment
Duration	15 minutes
Learning Objectives	• Understanding People at Risk • Understand the risk factors and preventive strategies • Understand treatment in human
Pre-requisite knowledge/skill	• Basic knowledge of vulnerable populations in infectious disease contexts. • Familiarity with environmental and occupational risk factors for vector-borne diseases. • Understanding of general treatment principles and antibiotic use in rickettsial infections.
Competencies to be achieved	• Capability to understand preventive measures for the control of scrub typhus • Understanding available treatments for human

PEOPLE AT RISK

People at risk of contracting scrub typhus are primarily those who live or work in rural, forested, or agricultural areas where infected chigger mites thrive. Farmers, agricultural workers, and laborers handling crops, bundling straw, or working in rice fields are particularly vulnerable due to their frequent exposure to mite-infested vegetation. Additionally, individuals engaging in outdoor activities such as camping, hiking, or visiting mite-infested areas are at increased risk. People living in endemic regions with poor sanitation and dense vegetation are also more susceptible. Awareness, protective clothing, and insect repellent use are essential in reducing the risk of infection.

PREVENTIVE MEASURES FOR GENERAL PUBLIC

1. Avoiding Mite-Infested Areas:

- Avoid walking or camping in areas known to have dense vegetation, tall grasses, or scrubland where mites commonly thrive.
- Be cautious in areas with heavy mite activity, such as rural, forested, or agricultural regions in endemic countries.

2. Wearing Protective Clothing:

- Wear long-sleeved shirts, long pants, and closed-toe shoes when venturing into mite-infested areas.
- Tuck pant legs into socks or boots to reduce skin exposure.
- Consider wearing light-colored clothing to easily spot any mites or chiggers.

3. Use of Insect Repellents:

- Apply insect repellents containing DEET (N,N-Diethyl-meta-toluamide) or permethrin to exposed skin and clothing.
- Permethrin-treated clothing and gear can offer additional protection as it repels and kills mites on contact.
- Reapply repellent as per the product instructions, especially in high-risk areas.

4. Environmental Control:

- Clear vegetation and brush around homes or campsites in endemic areas to reduce mite habitats.
- Use chemicals like acaricides (pesticides effective against mites) to treat vegetation in high-risk areas, particularly near human settlements or work areas.

5. Hygiene and Personal Protection:

- After spending time outdoors, shower and change clothes to reduce the risk of mite bites.
- Wash clothes in hot water and dry them on high heat to kill any mites that may have attached.
- Check for mite bites, as chiggers are small and their bites may go unnoticed until symptoms develop.

6. Education and Awareness:

- Educate at-risk populations, such as farmers, forestry workers, military personnel, and travellers, about the risks of scrub typhus and how to protect themselves.
- Raise awareness in endemic regions regarding the identification of mite habitats and protective measures.

7. Vaccination:

- Currently, no vaccine is available for scrub typhus. Research is ongoing, so preventive measures remain the most effective strategy.

8. Early Detection and Treatment:

- Promote awareness of the symptoms of scrub typhus (fever, rash, eschar) and the importance of seeking early medical treatment.
- Prompt diagnosis and treatment with doxycycline or azithromycin can prevent severe complications, but prevention remains crucial to avoiding infection

TREATMENT

When healthcare providers suspect that a patient might have a rickettsial infection, it is essential to initiate antibiotic treatment promptly without waiting for laboratory confirmation. At the primary healthcare level, several important steps need to be taken:

Recognition of Disease Severity: If a patient presents with complications from a potential rickettsial infection, immediate treatment with doxycycline, an effective antibiotic, should be initiated before referral to a higher-level healthcare facility.

Alternatives to Doxycycline for treating scrub typhus include azithromycin, commonly used for children and pregnant women due to its safety profile, and chloramphenicol, which is effective but less preferred due to side effects like bone marrow suppression.

Contraindications for Doxycycline involve pregnancy, children under 8 years (due to risks of tooth discoloration and bone effects), and allergy to tetracyclines. In cases where doxycycline is unsuitable, azithromycin is often the preferred option for pregnant women and children. Early and appropriate treatment is crucial, as untreated scrub typhus can lead to severe complications.

Referral for Complications: In cases where complications like Acute Respiratory Distress Syndrome (ARDS), Acute renal failure, Meningoencephalitis, or Multi-organ dysfunction are observed, the patient should be referred to a secondary or tertiary healthcare center. In addition to providing recommended care for these complications, treatment for scrub typhus with doxycycline should be administered.

Fever of Five Days or More: In cases of prolonged fever (lasting for five days or more) where other common febrile illnesses like malaria, dengue, and typhoid have been ruled out, the following medications should be considered:

For Adults: Doxycycline at a dose of 200 mg per day in two divided doses for individuals weighing above 45 kg, to be continued for seven days. Alternatively, Azithromycin at a dose of 500 mg in a single dose for five days. **Chloramphenicol at a dose of 500 mg every 6 hours for 7 days. However, the haematological side effects and Gory Baby Syndrome in premature neonates remains an important concern.**

For Pregnant Women: Azithromycin at a dose of 500 mg in a single dose for seven days. Azithromycin is preferred in pregnant women because doxycycline is not recommended during pregnancy.

For children with scrub typhus, doxycycline is administered at 2.2 mg/kg body weight twice daily for those under 45 kg, and 100 mg twice daily for those over 45 kg. Treatment should continue for at least 3 days after the fever subsides and until there is clear evidence of clinical improvement.

If the clinical signs and symptoms persist, healthcare providers should consider alternative diagnoses.

For complicated cases, the following treatment options can be initiated:

Intravenous doxycycline (if available) at a dose of 200 mg administered on day 1 and 100 mg twice daily for 6 days. Azithromycin at a dose of 500 mg twice daily for 1 to 2 days and 500 mg once daily for 7 days.

Intravenous chloramphenicol at a dose of 50-75 mg/kg/day, given in 6-hourly doses as an infusion over one hour initially, followed by oral therapy to complete a course lasting 7 days. Considering the toxicity of this drug, it should be kept as a reserve drug for situations when other drugs are not available or are contraindicated.

Management of individual complications should be done in line with established medical practices.

Recently an Indian study* observed a reduction of mortality by instituting a combination of intravenous doxycycline and azithromycin when compared to either of them alone in complicated severe scrub typhus cases. The authors used the combination therapy as per the following regimen –

- Intravenous doxycycline 200 mg twice daily on day one followed by 100 mg twice daily for 6 days
- Intravenous azithromycin 500 mg twice daily on first day followed by 500 mg daily for 6 days.
- It's important to note that in some regions of Southeast Asia, there have been reports of strains of the rickettsial bacterium that are resistant to doxycycline and/or chloramphenicol. However, these strains have shown sensitivity to azithromycin, making it a valuable alternative treatment option.

People at Risk



Farmer working in cultivated field



Bundling waste straw



Farmer working in vegetable field



Visiting Mite islands

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SCRUB TYPHUS

Prevention



Cover the body when visiting bushy/shrubby areas



Apply mite repellent (*Diethyltoluamide*) to exposed skin



Apply miticidal agent (*Benzyl Benzoate*) on clothing and bedding



Avoid sleeping on ground and mite and going to mite affected terrain



Treat the ground and vegetation with residual insecticides



Remove limited amounts of shrubs and low vegetation around the house



Control Rodent population



Regularly clean animal sheds

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SCRUB TYPHUS

Recognizing and Managing Severe Rickettsial Infection

· Disease Severity and Initial Treatment

• **Immediate Intervention:** Start doxycycline promptly in suspected rickettsial infection before referring to a higher-level facility.

· Alternatives to Doxycycline

• **Azithromycin:** Safer option for children and pregnant women.
• **Chloramphenicol:** Effective but limited due to risk of bone marrow suppression.

· Contraindications for Doxycycline

• Avoid in **pregnancy, children under 8 years** (tooth and bone risks), and those with **tetracycline allergy**.
• Use **azithromycin** for pregnant women and children if doxycycline is unsuitable.

· Referral for Complications

• Acute Respiratory Distress Syndrome (ARDS), Acute renal failure, Meningoencephalitis, Multi-organ dysfunction.
• Continue doxycycline while managing complications.

· Management of Fever Lasting Five Days or More

• In prolonged fever cases (over five days), where **malaria, dengue, and typhoid are ruled out**, doxycycline or appropriate alternative therapy should be initiated.

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SCRUB TYPHUS

Treatment



· The drug of choice for treating scrub typhus is **Doxycycline**.

Antibiotics are most effective if given soon after symptoms begin.

For Adults: Primary treatment of scrub typhus is Doxycycline at a dose of 200 mg per day in two divided doses for individuals weighing above 45 kg, to be continued for seven days. Alternatively, **Azithromycin** at a dose of 500 mg in a single dose for five days.

Chloramphenicol at a dose of 500 mg every 6 hours for 7 days. However, the hematological side effects and Gory Baby Syndrome in premature neonates remains and important concern

For Pregnant Women: Azithromycin at a dose of 500 mg in a single dose for 7 days. Azithromycin is preferred in pregnant women because doxycycline is not recommended during pregnancy.

For children: Doxycycline is administered at 2.2 mg/kg body weight twice daily for those under 45 kg, and 100 mg twice daily for those over 45 kg.

Treatment should continue for at least 3 days after the fever subsides and until there is clear evidence of clinical improvement.

If the clinical signs and symptoms persist, healthcare providers should consider alternative diagnoses.

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SCRUB TYPHUS

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- Intravenous doxycycline (if available) at a dose of 200 mg administered on day 1 and 100 mg twice daily For 6 days.
- Azithromycin at a dose of 500 mg twice daily for 1 to 2 days and 500 mg once daily for 5 to 7 days
- Intravenous chloramphenicol at a dose of 50-75 mg/kg/day, given in 6-hourly doses as an infusion over one hour initially, followed by oral therapy to complete a course lasting 7 days.
- Considering the toxicity of chloramphenicol, it should be kept as a reserve drug for situations when other drugs are not available or are contraindicated.
- **For Adults:** Primary treatment of scrub typhus is Doxycycline at a dose of 200 mg per day in two divided doses for individuals weighing above 45 kg, to be continued for seven days. Alternatively, **Azithromycin** at a dose of 500 mg in a single dose for five days.

SCRUB TYPHUS

Adult

- **Doxycycline:** 200 mg/day in two divided doses for individuals >45 kg (7 days)
- **Alternatives:**
- **Azithromycin:** 500 mg once daily for 5 days
- **or**
- **Chloramphenicol:** 500 mg every 6 hours for 7 days



- **Azithromycin** 500 mg in a single dose for 5 days



Children

- **Doxycycline:** 2.2 mg/kg body weight twice daily for those under 45 kg, and 100 mg twice daily for those over 45 kg
- **OR**
- **Azithromycin:** 10 mg/kg on the first day (maximum 500 mg), followed by 5 mg/kg daily for the next 4 days (maximum 250 mg/day).

SCRIB TYPHUS

Treatment Options	Description
Doxycycline	• Mainstay of treatment for most rickettsial diseases, including scrub typhus • Dosage: 200 mg per day in two divided doses • Duration: 7 days • Suspected doxycycline resistance reported
Azithromycin	• Excellent alternative, especially when resistance to doxycycline is suspected • Benefits: long tissue half-life, long-lasting post-antibiotic effects • Dosage: 500 mg in a single dose for 5 days • Efficient penetration of polymorphonuclear leukocytes and macrophages, which are target cells for <i>O. tsutsugamushi</i>
Chloramphenicol	• Another treatment option • Dosage: 500 mg every 6 hours for 7 days • Caution: Haematological side effects and Gory Baby Syndrome in premature neonates • Not a first-line treatment option • Consider as a second-line treatment option after excluding active tuberculosis

SCRIB TYPHUS

- Deranged laboratory parameters such as leucocytosis, thrombocytopenia, elevated transaminases, abnormal chest X-ray, and high serum creatinine levels are associated with a worse prognosis in severe scrub typhus.
- Patients with septic shock, hypothermia, and the aforementioned laboratory abnormalities are at higher risk for organ dysfunction and death compared to those with fever alone.
- Severe pulmonary involvement, including acute respiratory distress syndrome (ARDS), is associated with higher mortality rates in scrub typhus.
- Renal failure, indicated by a serum creatinine level greater than 1.4 mg, is a life-threatening complication and an independent predictor of fatality in scrub typhus.



SCRIB. TYPHUS

Prognosis And Follow-up continued....

- ICU management without an eschar and higher APACHE II score are independent risk factors associated with high mortality in severe scrub typhus.
- Initial high loads of scrub typhus DNA at the time of admission are correlated with higher mortality and longer illness duration.
- Limited studies and conflicting results make it challenging to establish definitive prognostic indicators for severe scrub typhus infection.
- Multiple organ dysfunction syndrome (MODS), including ARDS, myocarditis, liver failure, acute renal failure, encephalitis, and vasculitis-induced shock, are common presentations of severe scrub typhus.
- Delay in treatment for severe scrub typhus can result in a high mortality index, sometimes as high as 30%.

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SCRUB TYPHUS

Notes

Session-7

Surveillance & Outbreak Management

Course No. 007	Session 7: Surveillance & Outbreak Management
Duration	30 minutes
Learning Objectives	• Understand Surveillance and Outbreak Management. • Understand the Outbreak Investigation steps for scrub typhus
Pre-requisite knowledge/skill	• Basic understanding of public health surveillance systems and data reporting. • Familiarity with outbreak investigation procedures and field epidemiology. • Knowledge of steps involved in controlling and managing vector-borne disease outbreaks.
Competencies to be achieved	• Practical understanding of scrub typhus outbreak investigation and management • Understanding of common findings and recommendations on a scrub typhus outbreak

SURVEILLANCE

Surveillance is the ongoing systematic collection, analysis, interpretation, and dissemination of health-related data. Its purpose is to guide public health action to reduce disease incidence (morbidity) and death rates (mortality) and ultimately improve population health.

TYPES OF SURVEILLANCE

Public health surveillance can be classified based on **case focus, approach to data collection, and level of diagnostic certainty**:

a. Case-Based Surveillance

- Focuses on individual cases, particularly for notifiable diseases requiring timely reporting and follow-up.
- Allows for rapid public health intervention and case-specific tracking.

b. Surveillance by Approach

- This category includes three primary methods:
 - ◇ Passive Surveillance: Health care providers report cases to public health authorities when they encounter them in routine practice. This approach is less resource-intensive but may lead to underreporting.
 - ◇ Active Surveillance: Public health officials proactively seek out cases, often through direct contact with health facilities. It provides more comprehensive data but requires more resources.
 - ◇ Sentinel Surveillance: Utilizes specific sites, such as selected hospitals or clinics, to monitor disease trends within defined populations. Useful for studying specific conditions or outbreaks in targeted areas.

c. Surveillance by Level of Diagnosis

- Surveillance can also be organized by the diagnostic certainty level:
 - ◇ Syndromic Surveillance: Identifies patterns of symptoms instead of confirmed diagnoses, enabling early outbreak detection based on preliminary symptom patterns.
 - ◇ Presumptive Surveillance: Based on initial diagnoses, often using preliminary lab data or clinical assessment before full confirmation.
 - ◇ Lab-Confirmed Surveillance: Relies on laboratory-confirmed cases, providing the highest level of diagnostic accuracy but possibly delayed data due to testing.

APPLICATION AND RELEVANCE TO PUBLIC HEALTH

Understanding and utilizing different types of surveillance allows public health practitioners to tailor responses to the nature and spread of diseases. Each type serves specific needs:

- **Case-Based and Active Surveillance** are effective for diseases that require immediate public health action.
- **Sentinel Surveillance** provides valuable trend data for targeted populations.
- **Syndromic and Lab-Confirmed Surveillance** allow for both early outbreak detection and verification through confirmed diagnostics, balancing speed and accuracy.

CONTROL MEASURES

- **Rapid case identification by health-care workers can help provide prompt treatment:** The early diagnosis of acute scrub typhus can greatly reduce the chance of life-threatening complications and guide optimal therapy. States should consider planning for prepositioning diagnostic kits for scrub typhus, ahead of peak seasons, to actively detect and manage cases.
- **Public education on case recognition and personal protection will help in the identification and prompt treatment of cases:** Advocacy, awareness and education activities should be targeted at school children, teachers and women groups in endemic areas.
- **Rodent control and habitat modification:** Rodent control is a multidimensional activity that requires multisectoral cooperation. Different control strategies such as trapping, poisoning and use of natural predators are in practice. Rodent control is primarily the responsibility of agriculture sector - poisoning is a common practice.
- **Vector control:** Chiggers can be controlled by insecticide treatment of the vegetation/forest pathways. Several wildlife rehabilitation organizations encourage the natural form of rodent control through exclusion and predator support and preventing secondary poisoning altogether. Habitat modification such as good sanitation in and around buildings creates an environment that is less suited for rodent populations. This will make area less attractive to commensal rodents and thereby prevent new populations from recolonizing the habitat. Allowing weeds to grow around buildings also encourages rats and mice. Repeated increase in rodent population even after use of poisons is a good indication that habitat modification is needed.

OUTBREAK

An outbreak signifies the sudden and unexpected surge in the number of cases of a specific disease or health condition within a defined geographic area or population during a particular period. The baseline or endemic level of a disease refers to the usual number of cases present in a community. Deviations from this expected level may lead to outbreaks when the causative agent and susceptible hosts are present in sufficient numbers, and the agent can effectively transmit from a source to the susceptible hosts.

The necessity for an outbreak investigation is of utmost importance. Such investigations serve the crucial purpose of defining the outbreak's magnitude concerning time, place, and affected individuals. Furthermore, these efforts aim to determine the conditions and factors responsible for the outbreak, identify its etiology, suggest control measures, and formulate recommendations to prevent future occurrences.

When an outbreak is suspected, the local health team, including Primary Health Center (PHC) and Community Health Center (CHC) medical officers, plays a pivotal role in verifying the outbreak. The initiation of an Early Warning Signal (EWS) promptly reaches the District Surveillance Officer for swift action. This EWS submission, crucial for effective outbreak response, includes verification details and is transmitted using the fastest available route.

The responsibility for responding to an outbreak falls upon the PHC and CHC Medical Officer of the affected area, supported by the local health team. The District Surveillance Officer confirms the existence of the outbreak based on preliminary findings. Subsequently, the District Rapid Response Team (RRT) is deployed to conduct a thorough investigation.

Responding to an outbreak necessitates comprehensive efforts to understand its origin, identify high-risk groups and areas, and evaluate control measures. The District RRT, allocated specific resources by the district administration, requires a dedicated and functioning vehicle for prompt site visits, essential drugs and medical supplies for preliminary treatment, diagnostic reagents and kits for initial diagnosis, and facilities to transport collected samples. These resources collectively enhance the efficiency and effectiveness of the response efforts, crucial in mitigating the impact of the outbreak on public health.

OUTBREAK RESPONSE

Responding to an outbreak requires a comprehensive and systematic approach to effectively manage the situation. Key steps include:

- 1. Investigation:** It is crucial to investigate each outbreak and Early Warning Signal (EWS) report to understand the root cause, identify high-risk groups and areas, and assess the effectiveness of control measures.
- 2. Resource Allocation:** The District Rapid Response Team (RRT) should be provided with specific resources by the district administration to ensure a swift and effective response. This includes:
 - A dedicated and operational vehicle to enable rapid site visits.
 - Essential drugs and medical supplies to initiate preliminary treatment for affected individuals.
 - Diagnostic reagents and kits for conducting initial diagnoses on-site.
 - Facilities for transporting samples to laboratories for further analysis.

By implementing these measures, the district can enhance its capacity to respond to outbreaks and protect public health effectively.

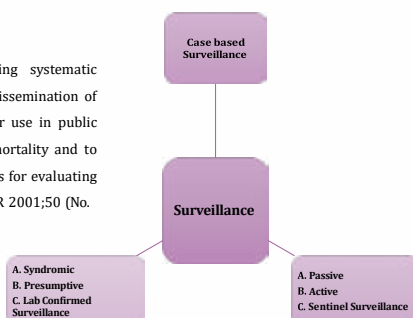
Methodology of Scrub Typhus Outbreak investigation by IDSP

The Rapid Response Team (RRT) plays a crucial role in managing scrub typhus outbreaks through several key activities:

- 1. Investigation and Interviews:** The RRT visits affected areas to conduct interviews with individuals who have tested positive for scrub typhus, gathering vital information about symptoms and potential sources of infection.
- 2. Rodent Capture:** Live traps are set up in the homes and cattle sheds of patients to capture rodents, as they are known carriers of the scrub typhus pathogen.
- 3. Sample Collection:** Dissections of captured rodents are performed to collect organs (heart, lungs, liver, and spleen), which are sent for culture analysis to detect the pathogen.
- 4. Collaboration with Health Officials:** The RRT organizes discussions with local health officers and staff to strategize on effective prevention and control measures.
- 5. Awareness Campaigns:** Information, Education, and Communication (IEC) activities are conducted to educate villagers and panchayat members about scrub typhus, its symptoms, and preventive measures.
- 6. Epidemiological Studies:** The RRT conducts epidemiological and environmental studies to understand the outbreak's factors, assessing conditions that may facilitate transmission.

These efforts aim to control the outbreak, reduce morbidity and mortality, and enhance community awareness to prevent future occurrences of scrub typhus.

Surveillance is defined as an "Ongoing systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and to improve health." (CDC. Updated guidelines for evaluating public health surveillance systems. MMWR 2001;50 (No. RR-13)



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SCRUB TYPHUS

1. Case based surveillance - is the practice of measuring and monitoring the occurrence, progression and outcome of a disease via the collection of patient-level data for a series of key events

2.A. Passive Surveillance - Regular reporting of disease data by all institutions that see patients (or test specimens) and are part of a reporting network is called passive surveillance.

2.A. Passive Surveillance - Regular reporting of disease data by all institutions that see patients (or test specimens) and are part of a reporting network is called passive surveillance.

2.B. Active Surveillance - Involves visiting houses, health facilities, talking to health-care providers and reviewing medical records to identify suspected cases of disease under surveillance.

2.C. Sentinel Surveillance- A sentinel surveillance system is developed to obtain more reliable and extensive disease related information that is not available through the reporting system. For example, USAID surveillance Data collection is well designed sentinel system

that is not available through the routine reporting, for e.g., H1N1 surveillance. Data collection in a well-designed sentinel system can be used to signal trends, identify outbreaks and monitor the burden of disease in a community, providing a rapid, economical alternative to other surveillance methods

other surveillance methods

3.A. Syndromic Surveillance - The fundamental objective of syndromic surveillance is to identify illness clusters early, before diagnoses are confirmed and reported to public health agencies, and to mobilize a rapid response, thereby reducing morbidity and mortality.

3.B. Presumptive Surveillance - Presumptive surveillance relies on diagnosis made on typical history and clinical examination by Medical Officers and presumptive lab tests.

Medical Officers and presumptive lab tests.

3.C. Lab Confirmed Surveillance - Relies on clinical diagnosis confirmed by an appropriate confirmatory laboratory test. The identification of new agents and changes in the behavior of micro-organisms especially in relation to susceptibility to anti-microbial are also important components of laboratory surveillance.

Center for the Study of the History of Mathematics

SCRUB TYPHUS

Early Diagnosis & Treatment

- Early identification of scrub typhus by healthcare workers can significantly reduce life-threatening complications.
- States should plan to **preposition diagnostic kits** for scrub typhus ahead of peak seasons to actively detect and manage cases.

Public Education & Awareness

- Targeted **awareness programs** for school children, teachers, and women's groups in endemic areas.
- Promotes **early case recognition** and **personal protection** to aid in prompt treatment.

- Rodent Control

- Multisectoral approach involving trapping, poisoning, and natural predators.
- Primarily managed by the agriculture sector, with a focus on responsible practices.

- Vector Control

- **Chigger management** through insecticide treatment on vegetation and forest pathways.
- **Habitat modification** through proper sanitation to reduce rodent populations.

Takeaway:

Takeaway:
Rapid case identification, public education, and environmental control are key to effective scrub typhus management.

Center for the Study of Health, WISC, 10/20/06

SCRIPTS TYPING

- An outbreak is a sudden and unexpected rise in cases of a specific disease or health condition in a particular area or population over a certain period.

- The number of a particular disease that is usually present in a community is referred to as the baseline or endemic level of the disease. Occasionally, the disease in a community rises above the expected level.

- Outbreaks occur when an agent and susceptible hosts are present in adequate numbers, and the agent can be effectively conveyed from a source to the susceptible hosts



Source: Ministry of Health and Family Welfare Government of India INTEGRATED DISEASE SURVEILLANCE PROGRAMME ToT TRAINING MANUALS FOR STATE/DISTRICT SURVEILLANCE OFFICERS, STATE RRTs & NODAL OFFICERS FROM MEDICAL COLLEGES Revised - 2020 70006419/2020/IO/D/IDSP-NCDC

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CRIBB TYPING

Need for outbreak investigation

The purpose of an investigation is to-

To define the magnitude of the outbreak in terms of time, place and person.

To determine the conditions and factors responsible for the occurrence of an outbreak or an epidemic.

To identify the etiology of outbreak and determine the measures of control and suggest recommendation to prevent future outbreaks.

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Outbreak Investigation

If an outbreak is suspected, the local health team (PHC/GHC medical officer) should verify the same. An Early Warning Signal will be submitted to the District Surveillance Officer by the fastest route to facilitate action.

The EWS should be submitted 2000419/2020/O/O IDSP-NCDC 11B 89 to the District Surveillance officer by the reporting unit as soon as verification of the suspected outbreaks made.

Who Should Respond to an Outbreak?

The PHC and GHC Medical Officer of the affected area along with local health team will be responsible for initial verification & response efforts in a suspected outbreak.

On the basis of preliminary findings, existence of outbreak is confirmed by District Surveillance Officer.

The District RRT will be deployed and will be responsible to investigate outbreak.

Source: Ministry of Health and Family Welfare Government of India INTEGRATED DISEASE SURVEILLANCE PROGRAMME To-T TRAINING MANUALS FOR STATE/DISTRICT SURVEILLANCE OFFICERS, STATE RHT & NODAL OFFICERS FROM MEDICAL COLLEGES Revised - 2020 2000419/2020/O/O IDSP-NCDC

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How to respond to an Outbreak?

Efforts should be made to investigate each and every outbreak /EWS. Investigations would reveal how the outbreak occurred, identify high-risk groups and areas, and evaluate control measures.

The District RRT will be allotted resources specifically for response related activities to be effective by district administration. They will need:

A dedicated and functioning vehicle so that they can visit the site at short notice.

Drugs and other medical supplies so that they can start the preliminary treatment.

Diagnostic reagents and kits for doing preliminary diagnosis.

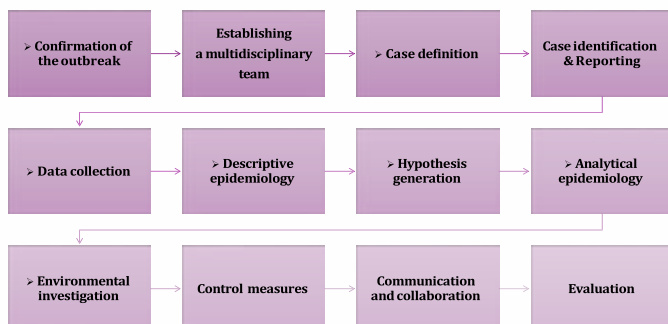
Facilities to transport the samples

Source: Ministry of Health and Family Welfare Government of India INTEGRATED DISEASE SURVEILLANCE PROGRAMME To-T TRAINING MANUALS FOR STATE/DISTRICT SURVEILLANCE OFFICERS, STATE RHT & NODAL OFFICERS FROM MEDICAL COLLEGES Revised - 2020 2000419/2020/O/O IDSP-NCDC

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Outbreak Investigation- Major steps



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Notes

ANNEXURES

Annexure 1 - (Weil-Felix Slide Method)

1. Blood sample is obtained by venipuncture and allowed to coagulate.
2. Centrifuged to allow the collection of a serum sample.
3. Place 50–100µl of patient serum on the slide.
4. Add a drop of desired antigen (Proteus OX19 or OX2 or OXK).
5. Mix the suspension by rotating the slide for 1 minute.
6. Visible agglutination indicates the positive test.



Source: Weil-Felix Test for Rickettsial Diseases: Introduction, Principle, Procedure, Result Interpretation and Remarks

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Notes

Annexure 2 - Weil-Felix Tube Agglutination Method

1. Take 18 round bottom tubes (6 each for OX2, OX19 & OXK). Prepare doubling dilution of serum from 1:20 to 1:320 and one negative control for OX2, OX19 & OXK each.
2. Label the tubes as 1-5 for serum dilutions of OX2, OX19 & OXK & 6th as negative control and add 0.5 ml of physiological saline to all tubes.
3. Prepare 1.5 ml of 1:5 serum dilution by adding 1.2 ml of normal saline & 0.3 ml of serum.
4. Add 0.5 ml of 1:5 serum dilution to 1st tube of each OX2, OX19 & OXK, that gives serum dilution of 1:10 in 1st tube of each OX2, OX19 & OXK.
5. Now transfer 0.5 ml from 1st tube of OX2, OX19 & OXK to 2nd, 3rd, 4th, and 5th tube and discard 0.5 ml from 5th tube each of OX2, OX19 & OXK.
6. Now tubes have doubling serum dilutions from 1:10 in 1st tube to 1:320 in 5th tube. Now add 0.5 ml of OX2, OX19 & OXK antigens to 1-5th tubes of 1st, 2nd & 3rd row respectively.
7. Incubate the tubes at 52°C in water bath for 4 hours.

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Annexure 3 - Procedure of ELISA

1. Well of each plate been coated with unique recombinant antigen mix.
2. The serum sample is diluted in sample diluent and applied to each well.
3. After incubation and washing, the wells of Scrub Typhus are treated with enzyme HRP-conjugate.
4. After a second incubation and washing step, TMB substrate is added.
5. An acidic stopping solution is added and the degree of enzymatic turnover of the substrate is determined by absorbance measurement at 450nm.
6. The absorbance measured is directly proportional to the concentration of IgM antibodies to scrub typhus antigen.



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Notes

[illegible]

The diagram illustrates the components of Personal Protective Equipment (PPE) and a person wearing them. The components are shown in individual icons with labels: Foot cover, N-95 respirator, Face Shield, Gloves, and Gown. Below these icons is a larger illustration of a person wearing a full PPE ensemble, with labels pointing to the 'N-95 Respirator Mask', 'Face Shield/ Goggles', 'Gloves', and 'Gown'.

Diagram illustrating the components of a leak-proof packaging system for hazardous waste:

- Sealed, designed primary receptacle
- Absorbent material
- Leakable, designed secondary receptacle
- Outer packaging
- UN Specification Mark

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NOTE TO FACILITATORS

This guide has been meticulously designed to enhance the understanding and expertise of doctors, veterinarians, paramedical staff, and laboratory personnel in dealing with scrub typhus cases. Your role is crucial in ensuring the success of this training, so please follow these instructions carefully:

Familiarize Yourself with the Content:

Thoroughly review all the materials provided in the scrub typhus training guide. This includes presentations, handouts, case studies and assessment tools.

Tailor the Training to Your Audience:

Understand the professional backgrounds of your participants (doctors, veterinarians, paramedics, and lab personnel). Tailor your examples and discussions to make the training relevant to their specific roles.

Set Clear Objectives:

Begin each session by clearly stating the objectives participants are expected to achieve by the end. This will give them a sense of direction and purpose throughout the training.

Create an Interactive Learning Environment:

Encourage active participation and open discussions. Use real-world scenarios to prompt critical thinking and problem-solving.

Use Multimodal Techniques:

Utilize a mix of teaching methods, such as presentations, group discussions and case-based learning. This will cater to different learning styles and keep participants engaged.

Encourage Questions:

Welcome questions and create a safe environment for participants to seek clarifications. This fosters deeper understanding and engagement.

Provide Regular Feedback:

Throughout the training, provide constructive feedback on participants' performance. This will help them identify areas for improvement and enhance their skills.

Summarize and Review:

At the end of each module, summarize key points and takeaways. Conduct a brief review to reinforce learning before moving on to the next topic.

Assessment and Certification: Develop an assessment mechanism, such as quizzes, practical assessments, or case presentations. Issue certificates of completion to participants who meet the training requirements.

Adapt to Participants' Pace:

Gauge the participants' pace of learning. Adjust the training speed accordingly, ensuring that everyone can follow and grasp the content.

Facilitate Networking:

Create opportunities for participants to interact and network with each other. This can lead to valuable knowledge exchange and collaboration.

Remember, your role as a trainer or facilitator is to guide participants through this comprehensive scrub typhus training with expertise, enthusiasm, and a dedication to enhancing their professional skills. Your efforts will contribute to building a more capable and knowledgeable medical workforce prepared to handle scrub typhus cases effectively.

Course Outline

It is imperative to underscore that the course outline harmonizes with the course schedule. Consequently, any modifications or adaptations made to the course schedule should be duly reflected in this course outline. This synergy between the schedule and the outline ensures consistency and alignment between training plans and their actual implementation.

NOTE: Make copies of the schedule, one for each participant and include in the training material bag.

Time	Topics/Activities	Training/Learning Methods	Resources/Materials
20 min	Welcome participants Facilitate introductions of participants Explore participants' expectations for the course	Open course with a word of welcome by organizers, lead trainers, etc. Facilitate the introductions of all participants and trainers. Explore participants' expectations for the course. Allow participants to freely explore their expectations. In the next session on review of the course objectives, address which expectations can be met and which cannot be met.	Prepare welcome sign, Name badges
20 min	Review course objectives and schedule. Review components of the training guide	Review the course goals and objectives; the course design and expected outcomes; Review the course schedule, including starting and ending times and times for breaks and lunch; Review the materials to be used in the course and ensure that participants understand the use of course materials.	Copies of course schedule, one for each participant from Facilitators' Guide (FG). Full set of the training guide: Facilitators' Guide (FG) Questionnaire
20 min	Assess participants' pre-course knowledge	Distribute the Pre-course Knowledge Assessment sheet to each participant. Ask them to answer each question. Allow 15 minutes for assessment. Immediately review the correct responses—Have participants grade the papers while the trainer reviews the correct answers with them and collect the papers after reviewing all the answers.	Pre-Training Quiz Sheet for each participant
4-5 hours	Presentation/ Discussion	Use the PowerPoint slides to present information	Power Point slides on the sessions planned as per agenda
20 min	Assess participants' post training knowledge	Distribute the Post Training Knowledge Assessment sheet to each participant. Ask them to answer each question. Allow 15 minutes for the Post Training Knowledge Assessment.	Copies of Post Training Knowledge Assessment Sheets (one for each participant)

Time	Topics/Activities	Training/Learning Methods	Resources/Materials
15 min	Course Evaluation	Ask questions of the participants and engage them in the presentation of the information.	
15 min	Closing	Closing remarks by training organizers. Distribute certificates to participants.	Certificate for each participant

PRE/POST TRAINING QUIZ

Instructions for the trainer:

- The trainer/instructor will administer the test before the training and collect the response.
- The same test will be given to the trainee after the completion of the training.
- The difference in scores will be recorded for training evaluation purpose.

Trainee Name:

Date:

Designation:

Test taken before the training (yes/no):

Test taken after the training (yes/no):

Instructions for the trainee:

- The test quiz carries 20 questions
- Attempt all the questions.
- Put a tick mark on the correct option or fill the blanks with True/ False
- Please check whether all questions are answered before submitting

- 1. What is the primary staining method effective for visualizing *Orientia tsutsugamushi* in laboratory settings?**
 - a. Gram staining
 - b. Giemsa staining
 - c. Acid-fast staining
 - d. Ziehl-Nielsen staining
- 2. What is the arthropod reservoir for scrub typhus, responsible for transmitting *Orientia tsutsugamushi* to humans?**
 - a. Ticks
 - b. Mosquitoes
 - c. Fleas
 - d. Chiggers
- 3. Which of the following is the primary reservoir host for *Orientia tsutsugamushi*, causing scrub typhus in the wild?**
 - a. Dogs
 - b. Cats
 - c. Mice
 - d. Birds

4. **What is the predominant surface protein of *Orientia tsutsugamushi*, crucial for serological diagnostics and vaccine development?**
 - a. Lipopolysaccharide (LPS)
 - b. TSA56
 - c. Peptidoglycan
 - d. Ankyrin-repeat protein
5. **What is the primary mode of transmission for scrub typhus to humans?**
 - a. Airborne particles
 - b. Human-to-human contact
 - c. Ingestion of contaminated water
 - d. Contact with infective larval mites
6. **Which geographical pattern is historically referred to as the region where scrub typhus is endemic, extending from Afghanistan in the west to Japan and the Pacific region in the east?**
 - a. Typhus Corridor
 - b. Orientia Belt
 - c. Tsutsugamushi Triangle
 - d. Mite Triangle
7. **What is a common consequence of reduced food intake due to anorexia and the energy expenditure associated with fighting scrub typhus infection in animals?**
 - a. Increased appetite
 - b. Weight gain
 - c. Weight loss
 - d. Muscle hypertrophy
8. **Which system in animals may respond to scrub typhus infection by developing palpable lymph nodes during physical examination?**
 - a. Respiratory system
 - b. Nervous system
 - c. Cardiovascular system
 - d. Lymphatic system

- 9. What aspect of scrub typhus in animals underscores the need for continued research and surveillance to understand its impact on wildlife and domestic animals?**
- Asymptomatic carriers
 - Ocular signs
 - Eschar development
 - Behavioral changes
- 10. What is a key clinical criterion for identifying a "suspected" case of scrub typhus?**
- Headache and rash
 - Acute undifferentiated febrile illness for five days or more
 - Elevated antibody titers in the Weil-Felix test
 - Presence of petechial lesions
- 11. Which diagnostic method confirms a "probable" case of scrub typhus, based on elevated antibody titers in the Weil-Felix test and enzyme-linked immunosorbent assay (ELISA)?**
- Polymerase chain reaction (PCR) testing
 - Indirect immune fluorescence assay (IFA)
 - Weil-Felix test
 - Computed tomography (CT) scan
- 12. What is required for establishing a "confirmed" case of scrub typhus, according to the case definition?**
- Elevated antibody titers in ELISA
 - Positive Weil-Felix test results
 - Detection of Rickettsial DNA in eschar samples or whole blood by PCR
 - Presence of a petechial rash
- 13. In the differential diagnosis of rickettsial diseases, which condition is characterized by a rash appearing on or about the 4th febrile day and spreading to the extremities, palms, and soles over several days?**
- Epidemic typhus
 - Murine typhus
 - Rocky Mountain spotted fever (RMSF)
 - Scrub typhus

- 14. What differentiates scrub typhus from murine typhus in the context of clinical manifestations?**
- a. Non-purpuric rash and extensive vascular complications
 - b. Presence of an eschar and satellite adenopathy
 - c. Rash developing in axillary folds and on the trunk
 - d. Mild disease with sparse vesicular rash resembling varicella
- 15. Which rickettsial disease is characterized by the development of multiple black eschars on the distal extremities with regional adenopathy?**
- a. Epidemic typhus
 - b. Rickettsial pox
 - c. African tick typhus
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- 16. What common features do scrub typhus, RMSF, and epidemic typhus share in terms of clinical manifestations?**
- a. Petechial rash
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 - c. Presence of eschar
 - d. Nonconfluent rash
- 17. Which laboratory method is particularly useful in the early stages of scrub typhus when antibody responses may not have fully developed?**
- a. Weil-Felix Test
 - b. ELISA
 - c. PCR (Polymerase Chain Reaction)
 - d. Culture
- 18. What is a significant consequence of increased urbanization and changes in land use patterns that contribute to the transmission of Scrub Typhus?**
- a. Decreased contact with natural reservoir hosts
 - b. Reduction in human density
 - c. Disruption of ecological balance
 - d. Limited exposure to infected chiggers

19. Which human behavior increases the risk of exposure to chigger-infested environments and contributes to the transmission of Scrub Typhus?

- a. Indoor activities
- b. Avoiding endemic regions
- c. Using insect repellent
- d. Trekking in endemic regions

20. In regions where strains of the rickettsial bacterium show resistance to doxycycline and/or chloramphenicol, what antibiotic has been identified as a valuable alternative for treating Scrub Typhus?

- a. Amoxicillin
- b. Ciprofloxacin
- c. Azithromycin
- d. Penicillin

ANSWER KEY

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