Naming of Rickettsiae and Rickettsial Diseases

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ABSTRACT: Over the last 20 years, advances in molecular techniques have greatly facilitated the identification of the members of the *Rickettsiales*, and numerous new species and diseases have been described. In this paper, we review taxonomic rules and appropriate approaches to valid naming of rickettsial species and the diseases they cause.

KEYWORDS: *Rickettsia*; taxonomy; genus; species; rickettsiosis; name

BACKGROUND

The *Rickettsia* are gram-negative obligate intracellular bacteria that have invertebrate hosts as vectors or reservoir hosts. Da Rocha Lima named the first species, *Rickettsia prowazekii*, which is the agent of epidemic typhus, in honor of Ricketts and von Prowazek, who both died of typhus while studying the disease.[1] The role of lice as vectors of *R. prowazekii* was demonstrated by Nicolle, who also described the first experimental infections with the organism and received the Nobel Prize for this work.[1] Wilson and Chowning first identified the role of ticks and tick bites in the

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transmission of Rocky Mountain spotted fever in their report in the *Lancet* in 1902,[2] and this suggestion was confirmed by Ricketts in his later publication in 1906.[3] Subsequently, Ricketts obtained the first isolate of *R. rickettsii* in guinea pigs and noted the similarity of *R. rickettsii* and the agent of epidemic typhus.[3] Wolbach was the first to clearly identify the intracellular nature of *Rickettsia* spp. in 1919.[4] In this paper, we review the contemporary taxonomic rules and appropriate approaches to valid naming of species of *Rickettsia* and the diseases they cause.

IDENTIFICATION OF BACTERIA

The first step in the identification of a bacterium is the assignment of the organism to a genus. Ideally, a bacterial genus consists of a group of species exhibiting similar genetic and phenotypic characteristics. It has been suggested that a genus includes bacterial species with DNA-DNA hybridization levels of 25 to 60%, degrees of 16S rDNA sequence similarity of > 90%, and G+C contents not diverging by more than 10%. The only real necessity for creating a new genus is when there is phylogenetic incongruence in these traits.[5]

A bacterial species reflects the sum of the biological information on a group of closely related strains isolated in pure culture. This information should include their taxonomic affinities, morphology, distribution, ecology, and pathogenicity. Initially, the identification of bacterial species was based on combinations of phenotypic criteria. The first genomic parameter used for taxonomic purposes was the G+C content; strains within a species should not have differences in G+C content of more than 5%.[6] Later, DNA-DNA hybridization techniques were introduced and a bacterial species included strains with DNA-DNA relatedness of ≥70 % and a ΔTm of ≤5%.[7] The latter method became the standard arbiter for the designation of genomospecies. The extensive use of 16S rDNA sequencing for identification of bacteria in environmental and clinical specimens has led to a dramatic increase in the number of potential new species.[8,9] It is currently considered that strains with more than 3% divergence belong to different species.[10]

Specific rules for recognizing, naming, and classifying species have been established which avoid redundant descriptions and the use of the same name for more than one species. Several prerequisites must be met before a new bacterial species is validated[11] (TABLE 1). Also, all information available should be included in its de-

TABLE 1. Prerequisites for the validation of bacterial species or subspecies

A.	The species concept only applies to bacteria which have been isolated in **pure culture**.
B.	To be as accurate as possible, the species description should be based on a minimum of **five isolates** for environmental bacteria.
C.	The new species should exhibit **both genomic and phenotypic discriminative** characteristics.
D.	A type strain should be identified for each new species, and should be made available to the scientific community through **two independent** official culture collections.
E.	The new bacterial name should appear in the **approved lists** of bacterial names.

scription, such as the structure, metabolic and reproductive features, and the biology of the organism. Bacterial isolates not meeting all the prerequisites should be referred to in quotation marks.

A subspecies is the lowest taxonomic rank that is recognized officially.[7] It contains closely related strains that have distinct phenotypic traits, but do not meet the genomic criteria required for classification as a distinct species.[7] The official validation of a subspecies is comparable to that of species.

NAMING OF BACTERIA

Scientists use taxonomic names when they communicate with one other. A species name is proposed by the first publication which meets the current requirement for designation of a species. The description of a new bacterial species should be based on well-characterized isolates, but there have been exceptions for organisms that are difficult to isolate in artificial culture, such as *Mycobacterium leprae*.

The current nomenclature for bacteria is based on the binomial naming system introduced by Linnaeus in the eighteenth century. Genus names begin with a capital letter and are written in italics. They are substantives or adjectives treated as substantives and are Latin or Latinized names. New genus names are followed by "gen. nov." Species names are composed of a binary combination of the genus name followed by an epithet indicating the species. The epithet begins with a small letter and is Latin or Latinized. The epithet may be derived from a person's name, a geographical location, or from any origin. It also may be composed of a combination of two or more names (e.g., *B. thetaiotaomicron*). For names derived from a geographical location, the Latin name should be used whenever possible or the modern name should be Latinized. The specific epithet must be treated as an adjective that must agree with the gender of the generic name (e.g., *Staphylococcus aureus*), as a substantive in apposition in the nominative case (e.g., *Desulfovibrio gigas*), or as a substantive in the genitive case (e.g., *Escherichia coli*). Species names are written in italics. New species names are followed by "sp. nov." Subspecies names are composed of a combination of the species name followed by "subsp." and an epithet indicating the subspecies. The subspecific epithet should be treated as specific epithets. Subspecies names are written in italics. New subspecies names are followed by "subsp. nov." Bacteria which cannot be cultivated but which fullfill genomic criteria to be classified as a species may provisionally be classified as *Candidatus.*[12] *Candidatus* names are derived in the same manner as species names but they are written in quotation marks instead of italics, and follow the word *Candidatus* in italics. For a more detailed description of the etymological guidelines used in naming a genus, species, or subspecies, we recommend readers to the exhaustive review by H.G. Trüper.[12]

RICKETTSIAE

The taxonomic classification of rickettsiae has long been a matter of controversy, and remains currently debated for some taxa. Taxonomic classification of members of the order *Rickettsiales* was originally based on relatively few phenotypic criteria.[13]

These bacteria are described as small, rod-shaped, Gram-negative, obligate intracellular organisms that retain basic fuschin when stained by the method of Gimenez.[13] They divide by binary fission, can be cultivated in living tissues, and are associated with invertebrate hosts that act as vectors and/or reservoirs. Initially, most bacteria with an obligate association with eukaryotic cells were included in the order *Rickettsiales* because they could not be classified with the phenotypic methods applied to bacteria that grew readily on artificial media. With the advent of 16S rDNA sequencing, several bacteria in the order *Rickettsiales* were reclassified. These included *Coxiella burnetii* and *Rickettsiella grylli*, which moved to the *Legionellaceae,*[14] *Eperythrozoon* sp. and *Haemobartonella* sp. to the *Mycoplasmataceae*,[15,16] *Wolbachia persica* to the γ-subdivision of *Proteobacteria* close to *Francisella* sp., and *Wolbachia melophagito* (Birtles and Molyneux, GenBank accession number X89110), *Bartonella* sp., *Rochalimaea* sp., and *Grahamella* sp. to the *Bartonellaceae.*[17] With the recent organization of the ehrlichiae,[18] the order *Rickettsia*les now comprises the family Anaplasmataceae which includes *Anaplasma*, *Ehrlichia*, *Neorickettsia*, and *Wolbachia*, and the family Rickettsiaceae which includes *Orientia*, *Rickettsia*.

Members of the *Rickettsia* are closely related phylogenetically and have a high degree of 16S rDNA nucleotide sequence similarity.[19,20] Historically, cross-reactions of patient's sera with somatic antigens of strains of *Proteus* OX19, OX2, and OXK were used to classify rickettsial isolates into 3 groups, respectively: spotted fever group, typhus group (TG), and scrub typhus group (STG). Subsequently, the only scrub typhus species, *R. tsutsugamushi*, was reclassified within the genus *Orientia.*[21] Other phenotypic criteria that have been used to describe *Rickettsia* species include the geographical distribution of the strain, the arthropod vector, pathogenicity in humans, mice, and guinea pigs, optimal culture temperature, time for plaque formation, size of plaques, growth in embryonated chicken eggs, and hemolytic activity.[22] However, the immunofluorescent antibody assay with acute phase sera of Swiss Webster mice developed by Philip in 1978 became the reference method for the identification of new SFG rickettsiae.[23] With this method, a rickettsial isolate is regarded as a new species if it has a specificity difference of ≥ 3 with all the other SFG rickettsia species. Thus, a species corresponds to a serotype. Since its introduction, this method has been considered a useful guide to speciation. However, opinions divide as to whether this holds true for all rickettsial strains. In addition, although useful, the method has several drawbacks including lack of reproducibility and the need to compare each new isolate with all previously described species.

With the advent of molecular classification, many of the currently accepted *Rickettsia* species were identified genetically before they were cultured in the laboratory. As is the case with other bacteria, *Rickettsia* can be given *Candidatus* status if they fulfill the genomic criteria but have yet to be cultured. Of the molecular classification techniques available, the DNA G+C content (32–33% for the SFG and 29% for the TG) and DNA-DNA re-association[7] are not easily applied to rickettsiae. Gene sequencing has become the most widely used method to identify rickettsial isolates.[19,24–27] However, no official rules have been adopted to classify these bacteria, in particular the boundaries of the genus and species status were confusing. This prompted an attempt to revise taxonomic rules applied to rickettsiae in order to clarify the status of all currently known rickettsiae, and to propose guidelines for the classification and denomination of rickettsial isolates. In particular, it was proposed to apply to rickettsial isolates gene sequence–based methods that are used for other

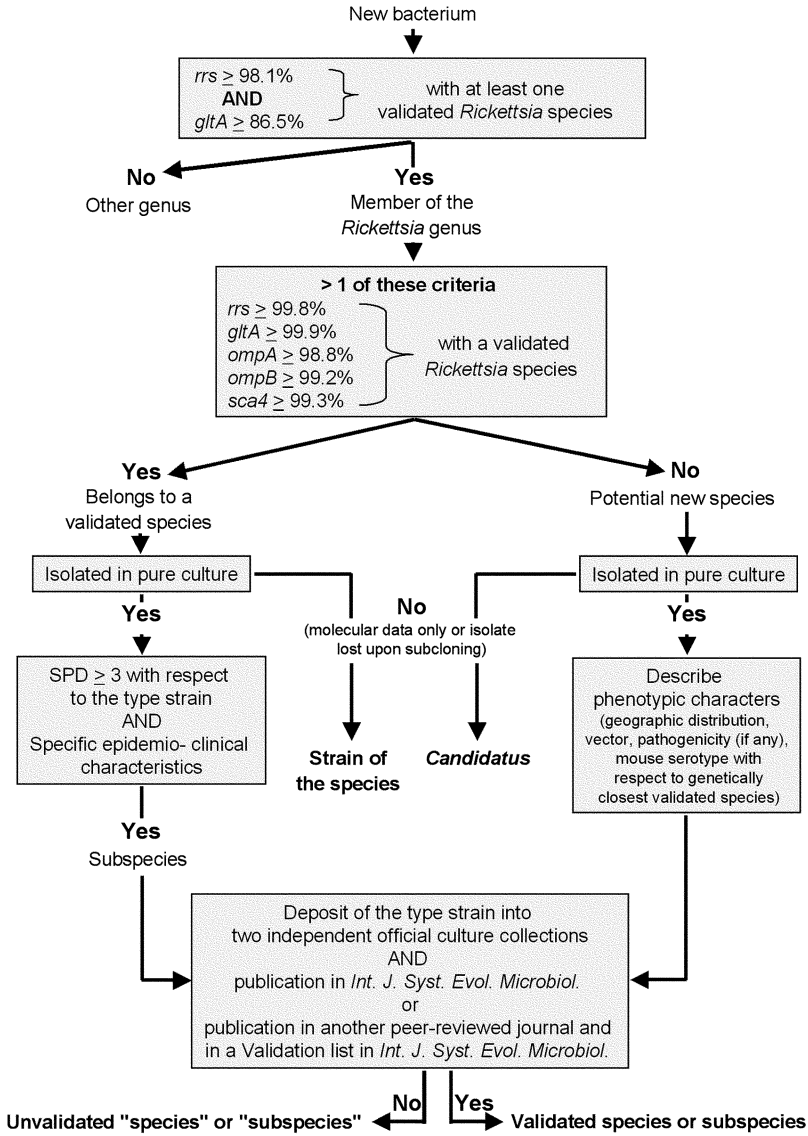

FIGURE 1. Taxonomic scheme for classification of rickettsiae at the genus and species levels. Genes: *rrs* encodes the 16S rRNA; *gltA* encodes the citrate synthase; *ompA* encodes the rOmpA; *ompB* encodes the rOmpB; *sca4* (gene D) encodes the PS-120. SPD = specificity difference in mouse serotyping.

bacteria. First,a method was proposed based on sequencing several genes, derived from the multi-locus sequence typing officially accepted as a taxonomic tool for other bacteria,[28] to provide genetic criteria to classify isolates at the group and species levels within the *Rickettsia* genus[29] (FIG. 1). The method was validated using 20 *Rickettsia* species that were uncontested and identified by serotyping with mouse antisera. The technique has enabled the demonstration that mouse serotyping does not always identify species that are genetically distinct.[29] In particular, it was demonstrated that rickettsiae closely related to *R. conorii* within the "*R. conorii* complex," and for which some authors disagreed as to whether these bacteria were distinct species or not,[30–32] belonged to the *R. conorii* species. However, as confusion persisted regarding the exact taxonomic status of these bacteria within the *R. conorii* species, a rule of the *ad hoc* committee on reconciliation of approaches to bacterial systematics[7] was used. This rule states that, even if related genetically, bacterial isolates within a given species could be considered as distinct subspecies if they differed phenotypically. When this rule was applied to the "*R. conorii* complex," it was observed that, although genetically homogeneous, rickettsial isolates within the *R. conorii* species had distinct genotypic, serotypic, and epidemio-clinical characteristics. Therefore, the creation of four *R. conorii* subspecies was proposed: "*R. conorii* subsp. *conorii*", "*R. conorii* subsp. *indica*", "*R. conorii* subsp. *caspia*" and "*R. conorii* subsp. *israelensis*".[33] With the use of similar criteria, the creation of two subspecies will soon be proposed within the *R. sibirica* species: "*R. sibirica* subsp. *sibirica*" and "*R. sibirica* subsp. *mongolitimonae.*"[34]

To be officially validated as a new species or subspecies, a rickettsia should fulfill the same requirements as other bacteria (TABLE 1). Also, sustained cell culture–adapted strains must be deposited in two collections from two different countries officially recognized by the World Data Centre for Microorganisms before they can be officially named. The American Type Culture Collection (ATCC) was the only official culture collection that accepted rickettsiae until our laboratory, the Unité des Rickettsies, was recently recognized as an official collection site by the World Data Centre for Microorganisms. The official description of uncultured species, such as *R. peacockii,*[35] should no longer be possible. Such rickettsiae should be classified as *Candidatus* "Rickettsia sp."

NAMING A *RICKETTSIA* SPECIES

The etymological rules used to name rickettsial species and subspecies and to give *Candidatus* status are the same as those used for other bacteria (see above). It is important to follow these rules carefully to avoid incorrectly Latinized names, as was the case with *R. canadensis* and *R. montanensis* (previously *R. canada* and *R. montana*). To date, 21 *Rickettsia* species have been officially validated (the Approved Lists of Bacterial Names is available online at <http://www.bacterio.cict.fr/>) (TABLE 2). The names of some species were derived from their geographical origin, mainly *R. africae*, *R. australis*, *R. canadensis*, *R. helvetica*, *R. japonica*, *R. massiliae*, *R. montanensis*, *R. sibirica*, and *R. slovaca.* The names of others were derived from the names of investigators who contributed significantly to the current knowledge on rickettsiae and rickettsial diseases. These include *R. aeschlimannii* (A. Aeschlimann), *R. belli* (E.J. Bell), *R. conorii* (A. Conor), *R. honei* (F.S. Hone), *R.*

TABLE 2. Validated species and subspecies of the genus *Rickettsia* and *Orientia*

Name	Former or Other names	Source of the Name	Investigators
R. prowazekii	R. prowazeki	Investigators	Ricketts and von Prowazek
R. typhi	R. mooseri	Clinical situation (typhos)	
R. rickettsii	Dermatocentro-xenus rickettsi	Investigator	Ricketts
R. conorii	D. conorii	Investigator	Conor
R. conorii subsp. conorii		Investigator	Conor
R. conorii subsp.indica	Indian tick typhus rickettsia	India	
R. conorii subsp.israe-lensis	Israeli spotted fever rickettsia, *R. sharoni*	Israel	
R. conorii subsp. caspia	Astrakhan fever rickettsia	Caspian Sea	
R. akari		Greek name of the mite vector	
R. africae		Africa	
R. japonica		Japan	
R. massiliae		Latin name of Marseille	
R. montanensis	R. montana	Montana	
R. canadensis	R. canada	Canada	
R. helvetica		Latin name of Switzerland	
R. sibirica		Siberia	
R. slovaca		Slovakia	
R. aeschlimanii		Investigator	Aeschlimann
R. parkeri		Investigator	Parker
R. bellii		Investigator	Bell
R. honei		Investigator	Hone
R. peacockii		Investigator	Peacock
R. rhipicephali		Tick vector	
R. felis	R. ctenocephali	Latin name of the cat, host of the flea vector	
R. heilongjiangensis	R. heilongjiangi	Heilongjiang (Chinese area)	
R. monacensis		Latin name of Munich	
R. australis		Australia	
Orientia tsutsuga-mushi	R. tsutsugamushi, R. orientalis	Orient, and Japanese name of the mite vector	

parkeri (R.R. Parker), *R. peacockii* (M.G. Peacock), *R. prowazekii* (S. von Prowazek) and *R. rickettsii* (H.T. Ricketts). Some species were named after their vectors, mainly *R. akari* ("akari" is Greek for mite) and *R. rhipicephali* (*Rhipicephalus sanguineus*). The agent of flea-borne spotted fever may have been first described as *R. ctenocephali* in 1918,[36] but is now called *R. felis* after the domestic cat (*Felis domesticus*), which is the host of *Ctenocephalides felis*, its flea vector. *R. typhi* was derived from the Greek term for "stupor" (*tuphos*), a symptom of typhus. The genus name of *Orientia tsutsugamushi*[21] (formerly *R. tsutsugamushi*), a bacterial species closely related to *Rickettsia* species within the family *Rickettsiaceae*, was derived from the Orient, where it was discovered and the species name was derived from the common name of the disease in Japanese ("tsutsugamushi," the mite disease). In addition to the validated species, as-yet unofficial species names have been published, mainly "*R. amblyommii*" [37] (also referred to as strain 85-1034, WB-8-2, or MOAa), named for its vector, *Amblyomma americanum*; "*R. monacensis*," [38] derived from the Latin name for Munich, Germany; "*R. heilongjiangensis*," [29] derived from the Heilongjiang province of China; "*R. texiana*," [39] derived from Texas; "*R. hulinii,*" [40] derived from the Hulin province of China; and "*R. thailandii*," [41] derived from Thailand. It should be noted that the latter two species names have been incorrectly Latinized and should be "*R. hulinensis*" and "*R. thailandensis*," respectively.

Of the four *R. conorii* subspecies that have recently been proposed, "*R. conorii* subsp. *conorii*" is named for an early rickettsiologist (A. Conor), while "*R. conorii* subsp. *indica*," "*R. conorii* subsp. *caspia*," and "*R. conorii* subsp. *israelensis*" are named for their geographic location. The two *R. sibirica* subspecies that will soon be proposed have also been named for their geographic locations; "*R. sibirica* subsp. *sibirica*" and "*R. sibirica* subsp. *mongolitimonae.*"

Although many new rickettsiae have been described on the basis of genomic criteria only, to date there are only two rickettsiae with recognized *Candidatus* status. The one is "*Candidatus* R. tarasevichiae,"[42] named in honor of I.V. Tarasevich, and the other is "*Candidatus* R. andeanae."[43]

Other rickettsial strains or amplicons that have been designated by strain names include *Rickettsia* sp. genotype cooleyi,[44] named after R.A. Cooley, and *Rickettsia* sp. strain cooperi,[45] named for its vector, *Amblyomma cooperi*. A number have been named according to their laboratory identification: *Rickettsia* sp. strain AT1;[46] *Rickettsia* sp. strain 364-D;[47] *Rickettsia* sp. strains RDa420 and RD1a440;[48] *Rickettsia* sp. strains ATT, HOT1 and HOT2;[49] *Rickettsia* sp. strain RpA4, DnS14 and DnS28;[50] *Rickettsia* sp. strain R300;[51] *Rickettsia* sp. strains IRS3 and IRS4;[52] and *Rickettsia* sp. strain AaR/SoCarolina (Kurtti *et al.*, unpublished material).

NAMING OF RICKETTSIAL DISEASES

To date, there have been no concrete rules for naming of diseases. A rickettsiosis is usually named by the first publication that describes its distinctive epidemiologic and clinical characteristics. It is not necessary for the causative agent to be identified, but a new disease may not be named with a description of a single patient, a clinical description only, or with only serological evidence. In general, a specific name has been given to the disease caused by each rickettsial species. Most commonly, rick-

ettsioses have been named for their geographical distribution and also their vector and/or clinical features: African tick-bite fever, Astrakhan fever, Flinders Island spotted fever, Indian tick typhus, Israeli spotted fever, Japanese spotted fever, Mediterranean spotted fever, North Asian tick typhus, Queensland tick typhus, and Rocky Mountain spotted fever. It is of note that the names of some of these rickettsioses do not reflect the position of their etiological agents in the typhus or spotted fever groups. Other rickettsioses have been named for their epidemiological features: epidemic typhus, endemic typhus, tick-borne lymphadenopathy (TIBOLA), flea-borne spotted fever, murine typhus, and scrub typhus. A few rickettsioses have been named for only their clinical appearance: lymphangitis-associated rickettsiosis (LAR)[53] and rickettsialpox.

To avoid confusion, it is preferable for each disease to have only a single name. Unfortunately, several names exist for older rickettsioses. North Asian tick typhus has also been named Siberian tick typhus, Mediterranean spotted fever has been named Marseilles fever or Boutonneuse fever, epidemic typhus has been named louse-borne typhus, and murine typhus has also been named endemic typhus. Although improvements in diagnostic and reporting methods should have prevented the situation, there are also recently described rickettsioses with several names: TIBOLA and *Dermacentor*-borne-necrosis-erythema lymphadenopathy (DEBONEL)[54] in Spain; Flinders Island spotted fever goes by the name Thai tick typhus in Thailand; Japanese spotted fever, and Oriental spotted fever.

In some cases, newly generated information has led to the name of a disease becoming inaccurate. Rocky Mountain spotted fever was initially described in the Rocky Mountains, but is now known to occur from Canada to South America; African tick-bite fever was initially described in sub-Saharan Africa but was subsequently identified in the West Indies. In these cases the original name of the disease has been maintained.

In conclusion, naming bacteria and their diseases is not only a matter of science and rules, but also a question of agreement among specialists in the field. The current proposal for initial name generation reflects the state of the art of the scientific tools applicable to these organisms. It is not a rigid system but a flexible model that will be developed upon the time as scientific knowledge is evolving.

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