

Current Research of Chlamydial Infection Diseases in China

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To the Editor: *Chlamydia* organisms belong to intracellular bacterial pathogens which are responsible for a range of human diseases, including trachoma, sexually transmitted disease, pneumonia, and other diseases.^[1-5] Some *Chlamydia*-infected diseases were old and had long time impacted on the people's health in China and worldwide, but people cannot put enough emphasis on it in local areas.^[6] For example, although China had reached the goal of eliminating blinding trachoma in 2015, some sporadic cases also exist in rural counties. Moreover, few of studies were conducted on pneumonia induced by *Chlamydia* in China due to the present low prevalence and the limited detective methods. Sexually transmitted *Chlamydia trachomatis* infection also has notorious effects on reproduction, often asymptomatic and recurrent; thus, chlamydial infection diseases remain important public health concern over its prevention and control. This article focuses on the importance of caring about *Chlamydia* spp. and discusses taxonomy, prevalence, and laboratory diagnosis methods of *Chlamydia* diseases in China.

Chlamydiae comprises 11 species that are pathogenic.^[7] *C. trachomatis* and *C. pneumoniae* are the two major species easily infected by humans, and others are zoonotic and always transmitted from animals to humans.^[8-11] Table 1 lists the six kinds of most common *Chlamydia* species and related diseases. *C. trachomatis* have different serovars: A, B, Ba, and C lead to trachoma, D to K lead to genital tract *Chlamydia* infection, and L1–L3 lead to lymphogranuloma venereum. All the species, other than *C. abortus*, can induce community-acquired pneumonia (CAP) in humans [Table 1].

Chlamydia spp. has two kinds of life forms related to infection: the elementary body (EB) and the reticulate body (RB). Among them, EB is the main body of infectious stage and RB is related to the replicative form. The host cell is invaded by EB of *Chlamydia* and then EB is transmitted to RB. Its replication is induced by binary fission and is released out with infectious EB by redifferentiation.^[12] EB maintains structure by disulfide-bridge protein complex. The feature explains the resistance of *Chlamydia* spp. to antibiotics targeting bacterial cell wall biosynthesis, such as penicillins.^[13] Genome structure and virulence are different among species.^[14]

Trachoma was important blindness disease in China in the last century. The pathogen of trachoma was first observed by FF Tang

in 1956 by cell culture in chicken embryo. In liberation stage, nine out of ten people were caught in trachoma. Through surgery for trichiasis, antibiotic treatment, face washing, and environmental improvements strategy, the prevalence of trachoma has sharply declined in recent decades.^[15] In 2015, it was pronounced that trachoma has been eliminated in China (prevalence <5%). Nowadays, only sporadic cases were found in local areas, such as Qinghai province.^[16] Some other countries [Table 1] also have existing trachoma and the prevalence was ranged from 4.7% to 43.9%, while China has low morbidity of trachoma in developing countries. Australia is the only highly income country with persisting endemic trachoma.^[17-23] *C. trachomatis* serotypes differ across regions. Serotype B was common in China and other countries in Asia, while serotype A, Ba, and C were more popular in Tanzania, Brazil, Morocco, North Africa, and Australia^[6,24] [Table 1].

The prevalence of pneumonia due to *C. pneumoniae* was reported to be much lower nowadays than previous years.^[25,26] Different countries had variable morbidity, from 1.4% to 8.0% listed in Table 1.^[25,27-30] In China, *C. pneumoniae* was found in 3.5% of CAP cases in children and 2.7% in adults. China had less disease prevalence than some other developing countries [Table 1]. Other *Chlamydia* spp. can induce pneumonia, including *C. trachomatis*, *C. psittaci*, *C. caviae*, and *C. felis*. *C. trachomatis* can also be transferred from cervix to amniotic cavity or via the placenta.^[8-10,31]

There are approximately 100–150 million new *C. trachomatis* cases occurring annually worldwide, affecting 68 million females.^[32,33] 75–90% of the patients usually do not exhibit any symptoms in both men and women.^[34] In 20–40% of untreated women, *C. trachomatis* may reach the fallopian tubes via the endometrial epithelium and cause pelvic inflammatory disease, and this silent infection can lead to tubal factor infertility, miscarriage, or ectopic pregnancy, which is

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Table 1: Taxonomy of *Chlamydia* spp., the associated diseases, typing methods and epidemiology

Pathogen	Host	Serotyping method designation	Target loci	Discrimination type
<i>C. trachomatis</i>	Human	MOMP serotyping	<i>ompA</i>	Immunoreactivity
		ELISA	<i>ompA</i>	Immunoreactivity
		MLST	7 house keeping genes	SNPs
		Real-time PCR	<i>ompA</i> + <i>pmpH</i>	SNPs + indels
		PCR-sequencing	<i>ompA</i>	SNPs
		PCR-RFLP	<i>ompA</i>	DNA restriction patterns
		PFGE	Genomic DNA	SNPs
<i>C. pneumoniae</i>	Animal and human	Whole-genome sequencing	Genome	All polymorphisms
		Do not need serotyping		
<i>C. psittaci</i> , <i>C. caviae</i> , <i>C. felis</i> , <i>C. abortus</i>	Animal-to-human transmission	Do not need serotyping		

Pathogen	Diseases	Countries	Prevalence	Population	Main serotypes	
<i>C. trachomatis</i>	Trachoma	Australia	15.4–43.9%	Children	Ba/C	
		Iran	5.9–10.8%	Children	B/C	
		Niger	10.0%	Children	Ba	
		India	35.0%	>15 years old	B/C	
		Gambia	6.7%	Children	Ba	
		Tanzania	32.3%	Children	A	
		Ethiopia	35.6%	Children	Ba	
		Brazil	4.7%	Children	A	
	China	<5.0%	Children	B		
	Genital tract chlamydia infection	China	2.1% (men)/2.6% (women)	Adults	E, F, G, D	
	LEV	Netherlands	0.9%	Men who have sex with men	L1–L3	
		UK	0.9%			
	<i>C. pneumoniae</i>	Pneumonia		7.2%	Infants	E, F, J, D, K, G, H
Pneumonia		German		1.4%	Adults	
		Brazil		5.2%	Children	
		United States		8.0%	Adults	
		Canada		8.0%	Adults	
		China		3.5%	Children	
Asthma, arthritis, cerebrovascular disease, atherosclerosis		Seldom research				
<i>C. psittaci</i>		Pneumonia	Worldwide	1.0%		
<i>C. caviae</i> , <i>C. felis</i>		Pneumonia	Seldom research			
<i>C. abortus</i>		Abortion, stillbirth, septicemia	Seldom research			

SNPs: Single-nucleotide polymorphisms; PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism; MOMP: Major outer membrane protein; MLST: Multilocus sequence typing; PFGE: Pulsed-field gel electrophoresis; LGV: Lymphogranuloma venereum.

a life-threatening condition.^[35,36] Untreated or inadequately treated patients also risk spreading the infection to sexual partners. It is estimated that 5 out of 1000 *C. trachomatis*-infected women will develop tubal factor infertility.^[37] In males, epididymitis is the most severe complication.^[33] In 2014, there were 1,441,789 chlamydial infections reported to the US Centers for Disease Control and Prevention in 50 USA states and the District of Columbia, which represents a 2.8% increase compared with the past 2 years. In China, using a national stratified probability sampling technique and urinary ligase chain reaction diagnostics, Parish *et al.* found relatively high prevalence per 100 population of 2.1% among men and 2.6% among women aged 20–64 years for genital chlamydial infection, and chlamydial infection is much more common than gonorrheal infection in the general population.^[38] The prevalence of chlamydial infection among sex workers is 32%.^[39] Genital *C. trachomatis* infection also promotes the transmission of HIV and is associated with cervical cancer. Detecting nucleotide sequence differences in the major outer membrane protein gene (*ompA*) of the different serovars is the new routine method to classify different strains of *C. trachomatis*. E, F, and D account for up to 60–70% of

the infection.^[40] Genotypes with E (27.9%), F (23.5%), G (12.4%), and D (11.1%) were most prevalent in China.^[41]

Asthma, arthritis, cerebrovascular disease, carotid atherosclerosis, age-related macular degeneration, and abortion can also be induced by *Chlamydia* spp.^[1-3,5,42]

The trachomatous inflammation-follicular could alternatively be due to organisms other than *C. trachomatis*.^[24,43] Copan swabs were recommended for sample collection.^[44] Several testing methods, such as culture, serology, immunofluorescence test, complement fixation test and PCR were applied in detection. The strain can only be acquired through cell culture.^[45] Although nucleic acid amplification techniques were highly sensitive and specific and were used widely in recent years, some new methods such as anti-Pgp3 antibodies of dried blood spots have been developed.^[24,31,46,47] According to different targets, several typing methods were applied, too [Table 1]. Among them, only whole-genome sequencing targets all polymorphisms, others target *ompA* or single-nucleotide polymorphisms.^[9,24]

For the laboratory diagnosis of *C. pneumoniae*, lower respiratory specimens were needed for detection, not swabs. To identify *C. pneumoniae* from other respiratory organisms, multiplex polymerase chain reaction was recommended [Table 1].

Nucleic acid amplification tests are currently recommended method to detect genital tract *Chlamydia* infection.^[48] Noninvasive sampling (urine or vaginal) is as effective as invasive sampling of vaginal, endocervical, or penile urethral swab and is more acceptable to patients. Rectal and oropharyngeal *C. trachomatis* infection can be diagnosed by testing at the anatomic site of exposure.

To decrease the number of *C. trachomatis* patients, oral azithromycin or topical tetracycline was used in endemic communities. However, some studies reported that *Chlamydia* isolates were heterotypic resistance to macrolides (including azithromycin) *in vitro*. The World Health Organization recommends mass drug administration for infection control and should continue until the prevalence of trachomatous inflammation-follicular in falls below 5% in subdistricts or community clusters.^[13,49]

C. pneumoniae is generally considered susceptible to antibiotics interfering with prokaryotic DNA, RNA, or protein synthesis, such as quinolones, tetracyclines, and macrolides, but in contrast to *C. trachomatis*, it was not sensitive to trimethoprim or sulfonamides.^[13]

For uncomplicated genital *Chlamydia* infection, treatment with single-dose azithromycin or 7 days of doxycycline for men and nonpregnant women is recommended, with doxycycline less preferred because of compliance issues.^[50] It has demonstrated >95% microbiological cure after 2–5-week therapy, with few antimicrobial resistances being documented and no examples of natural and stable antibiotic resistance in strains collected from humans.^[51]

Due to the intracellular characteristics of *Chlamydia* spp., it is difficult to culture and get the strains of the *Chlamydia* spp., so vaccine was not available for *Chlamydia* diseases now. Acquired immunity to reinfection is serovar specific, weak, and short lived. Although the prevalence of *Chlamydia* diseases is sporadic in local areas, limitation of detective method in the areas may be the reason, not real representation of diseases. Hence, *Chlamydia* spp. and the associative diseases are worth to be noticed in future, especially in developing countries.^[52]

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