□総説□

Burden of four curable sexually transmitted infections in Japan and the research gaps: a systematic literature review

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Abstract

Purpose: We aimed to map and synthesize evidence on the burden of four curable STIs (chlamydia, gonorrhea, syphilis, and trichomonas) in Japan using a systematic literature review and to identify the research gaps.

Methods: According to the pre-defined criteria, PubMed and ICHUSHI databases were searched for studies conducted in Japan. Target populations included patients with at least one of the curable STIs of interest who were adolescents or older. Target outcomes included epidemiology, treatment, economic, and humanistic burdens.

Results: A screening of 935 references and complementary hand-search identified 48 references reporting epidemiological (*n*=31), treatment (*n*=13), and economic burdens (*n*=8). No relevant studies assessing humanistic burdens were identified. Chlamydia was the most studied STI (*n*=28), followed by gonorrhea (*n*=27). The national surveillance showed continuous decreases in notifications of chlamydia and gonorrhea by sentinel sites over the years; however, potential unrepresentativeness of the sentinel sites was suggested based on data from some studies. Reports on prevalence, co-infection, and asymptomatic rates revealed a wide range of rates that were highly dependent on the population characteristics such as comorbid status and gender. The recent rise of decreased in vitro gonorrhea susceptibility to ceftriaxone was observed in several studies. Data on economic and humanistic burdens and on commercial sex workers were limited.

Conclusion: The overall mapped evidence underscored the importance of further considering variability in patients' characteristics such as vulnerability, treatment accessibility, and asymptomatic rates, enhancement of antimicrobial resistance surveillance systems, and fulfilment of research gaps due to data scarcity.

Keywords：burden of illness, sexually transmitted infections, systematic literature review

Ⅰ. Introduction

Sexually transmitted infections (STIs) have continuously burdened the world[1)]. Of 30 sexually transmitted pathogens, four of the most common curable STIs are *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), *Treponema pallidum subspecies pallidum* (TP), which causes syphilis, and *Trichomonas vaginalis* (TV)[2)].

The global estimates performed by the World Health Organization (WHO) in 2012 indicated that the four curable infections accounted for 357 million new infections in adults, the decrease was observed in 2012 compared to the previous years: 2005 and 2008[3)].

To tackle these STIs in Japan, the following appropriate treatments have been advised by the diagnosis and treatment of STIs 2016 guidelines[4)]. However, a recent increase in the incidence of TP since 2010 has been reported by the National Institute of Infectious Diseases (NIID) of Japan[5)].

To end the public health problem of the STI epidemic, the WHO has established the global health sector strategy on STIs 2016–2021, which contains five main strategic directions such as strengthening a robust strategic information system to review the current status and burden[6)]. Studies extensively reviewing such information of the four curable STIs in Japan are scarce although such evidence is

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indispensable in understanding the entire picture of STIs to enact a tailored response. This study aimed to map and synthesize the currently available evidence related to the burden of illness through a systematic literature review using preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[7], and to identify research gaps on the four curable STIs in Japan.

Ⅱ. Materials and Methods

1. Data sources

To retrieve the relevant records, we searched for literature in the bibliographical databases of PubMed and Igaku Chuo Zasshi (ICHUSHI), the latter of which is the largest Japanese medical literature database. The last search using the defined search strategies was performed on December 5, 2019.

In addition to the bibliographical databases, the search was complemented with gray literatures such as Japanese guidelines and the websites of the related societies and research institutions such as the Japanese Society for STIs, the Japanese Association for Infectious Diseases, and the NIID.

2. Eligibility

The search in the bibliographical databases was conducted according to the search strategies defined with search terms that were selected based on the pre-defined PICOS inclusion and exclusion criteria (P: population, I: intervention, C: comparator, O: outcomes, and S: study design; Appendix 1). The population of interest was patients with at least one of the curable STIs of interest (i.e., CT, NG, TP, or TV) who were adolescents or older. No specific criteria were applied for the intervention or for comparator. Outcomes of interest included epidemiological, treatment, economic, and humanistic burdens. The relevant study designs included observational studies, database analyses, and economic evaluations. Japanese studies published in English or Japanese were included. Records were searched from 2010 onward for epidemiological and treatment outcomes to align with the recent trend of increases in STIs observed since the early 2010s by the NIID[5]. No timeframe or study setting criteria were applied to the studies with economic and humanistic outcomes to maximize the evidence generation given how few studies estimated these outcomes. All the records identified through different bibliographical databases were imported to a joint EndNote library, and the duplicates were removed before being exported to an Excel spreadsheet.

3. Study selection process

The study selection was performed in a two-step process using an Excel spreadsheet: the titles and abstracts were first reviewed, followed by a review of the full-texts. The title and abstract review was conducted by a reviewer to identify records satisfying the inclusion and exclusion criteria. All included records then underwent a full-text review by a reviewer. Records and full-texts were excluded for the following reasons: “not relevant population,” “not relevant outcome,” “not relevant study design,” “not relevant language,” “not relevant geographical scope,” “not relevant setting,” “not relevant timeframe,” and “duplicates.” Another independent reviewer performed quality control on the study selection process. The flow of the study selection process through the different steps followed the PRISMA flow diagram[7].

4. Data extraction process

For the selected studies, the data of interest were extracted using Excel software comprising six sheets: study characteristics, population characteristics, and one sheet for each of the outcomes. Studies published in Japanese were translated into English during extraction. When relevant data were available only in figures, numbers were deduced using Engauge Digitizer Software for data extraction[8]. Another independent reviewer performed quality control on the data extraction process.

Ⅲ．Results

1. Selected studies

The bibliographical database searches resulted in the retrieval of 935 records. After removing 125 duplicate articles, 810 records were included for the title and abstract screening. The title and abstract screening excluded 685 records based on the PICOS criteria. Thus, 125 references were included in the full-text review. After excluding 80 full-texts and adding three references identified through the complementary search, we finally selected 48 references. The flow chart of the study selection is shown in Figure 1.

Most of the studies reported epidemiological outcomes (*n*=31), followed by treatment (*n*=13) and economic outcomes (*n*=8). No studies reported humanistic outcomes. The most frequent study design among the identified studies was cross-sectional (*n*=37), which included 23 studies

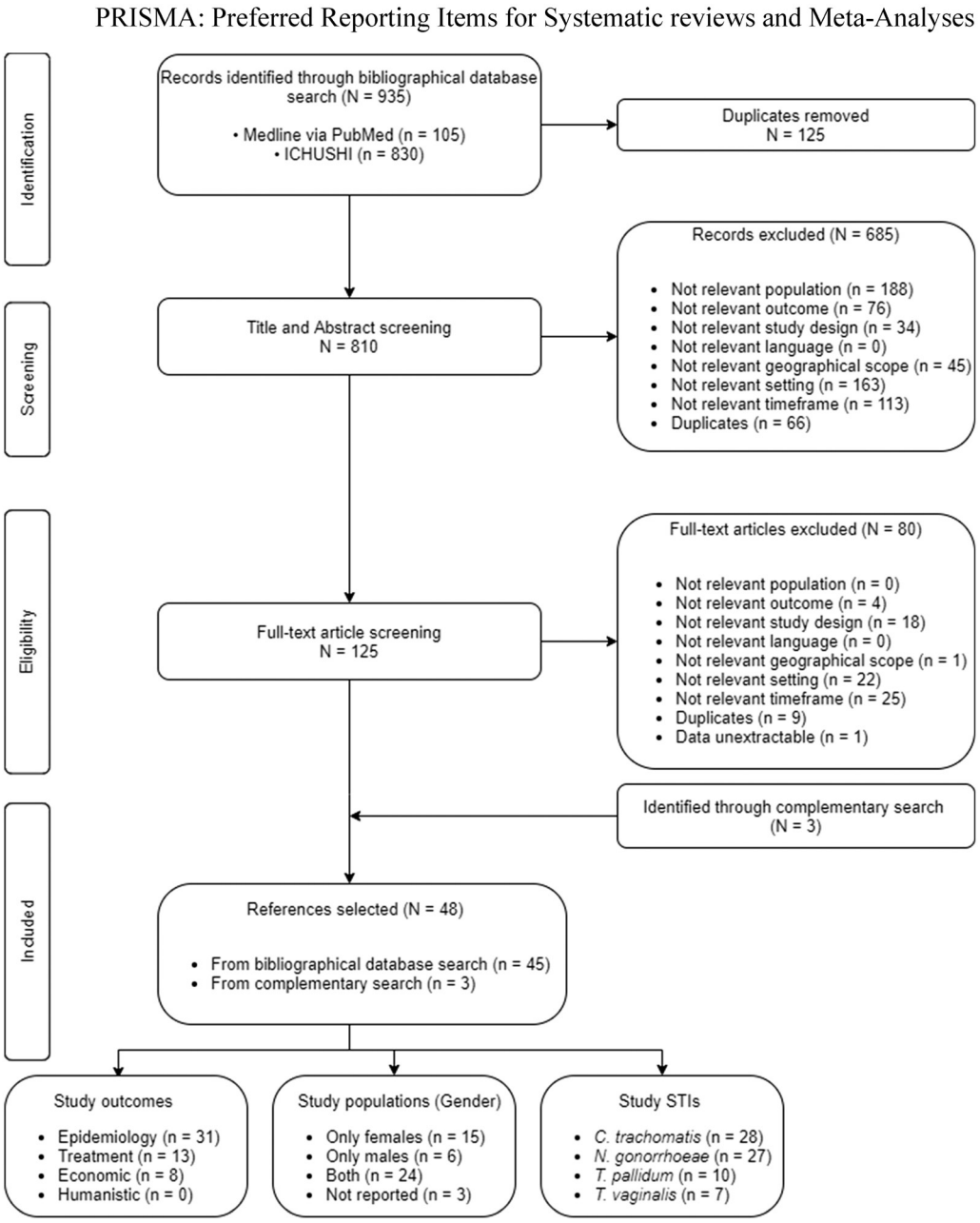

Figure 1　PRISMA flow chart of the study selection process.
The last search was performed on December 5, 2019.

conducted under surveillance studies, followed by four prospective observational studies and two retrospective observational studies. Five case series were included only for economic outcome data.

2. Study population

CT was the most studied STI among the four curable STIs of interest (*n*=28), closely followed by NG (*n*=27). Fewer studies were identified that evaluated TP (*n*=10) and TV (*n*=7). Twenty-four of the 48 studies included both female and male individuals, 15 included only females, and six included only males. Three studies did not report any information related to gender. There was a higher frequency of female-only studies on TP and CT; however, the female-only and male-only studies on NG and TV were evenly distributed. Except for the 19 studies that lacked age-related information, individuals aged 20−29 years old were the most commonly studied age range (*n*=20), followed by individuals 30−39 years old (*n*=9).

3. Synthesis of results by specific outcome

1) Epidemiological burden

A total of 31 studies reported on the epidemiological burden with the following outcomes: prevalence and incidence (*n*=23; 17 on CT, 10 on NG, 5 on TP, and 3 on TV), co-infection (*n*=9; 9 on CT, 7 on NG, 2 on TP, and 4 on TV), asymptomatic (*n*=6; 5 on CT, 5 on NG, and 1 on TP), pregnancy-related (*n*=3; 3 on TP), and mortality (*n*=1; 1 on CT).

Complete survey data from the National Epidemiological Surveillance of Infectious Diseases (NESID) program revealed that 621 new all-stage TP cases (0.48 per 100,000 population) were reported in 2010. This number continuously increased over the years, resulting in 7,007 cases in 2018 (5.5 per 100,000 population)[5, 9]. The incidence rates of CT in females and NG in males were estimated by Tanihara et al. based on the monitoring results of sentinel sites under the NESID program[10]. The results are plotted in Appendix 2 along with two other studies that aimed to exhaustively investigate CT and NG occurrences in all medical facilities of their scopes[10, 11]. The highest NG and CT incidence rates were consistently shown in the 20- to 29-year-olds, followed by those aged 30−39. Overall, the results estimated based on the NESID tended to demonstrate the lowest values by 100,000 person-years compared to other studies. The discrepancies between the highest and lowest values were more important in the population with high incidence rates (1184.2 vs. 213.3 in females with CT and 266.0 vs. 95.3 in males with NG in patients 20 to 29 years old).

The prevalence studies revealed a wide range of rates that were highly dependent on the type of study population evaluated for each STI (Table 1). Higher prevalence rates were observed for CT compared to NG, TP, and TV overall. Patients with human immunodeficiency viruses (HIV) were the most vulnerable population for CT and TP infections (57.7% patients with HIV had CT and 35.1−46.8% patients with HIV had TP)[12, 13]. Available gender-specific data showed the highest prevalence of TP (46.8%) in the men who have sex with men (MSM) population with HIV[12]. Consistent high prevalence rates of CT, NG, and TV were reported in male patients with urethritis (21.5−37.0% with CT, 30.4% with NG, and 3.3% with TV)[14, 15]. Studies including only female individuals revealed relatively higher rates in women with obstetrics and gynecology (OB-GYN) visits for probable medical care (5.9−9.6% with CT and 2.1−11.0% with NG)[16, 17]. Notably, a study including asymptomatic female university students revealed a CT infection rate of 3.7%[18]. A wide range of rates were noted globally in the results reported by public health programs (PHPs) related to HIV and STIs[13, 19-22] and in testing laboratories that received specimens from varied sources such as internet-accessed STI testing[23-27].

The most frequently reported co-infection rates were noted for CT in NG patients (*n*=7), followed by NG in CT patients (*n*=6), with higher rates observed for co-infections

Table 1　Prevalence of the curable STIs of interest in the different types of study population.

Population type	Population definition	*C. trachomatis*	*N. gonorrhoeae*	*T. pallidum*	*T. vaginalis*
HIV[12, 13)]	HIV-positive patients (Overall)	57.7%	n/a	35.1−46.8%	n/a
	MSM subgroup	n/a	n/a	46.8%	n/a
PID[37)]	Females diagnosed with PID +/− TOA and admitted to hospitals	2.1%	0.6%	n/a	n/a
Urethritis[14, 15)]	Males with urethritis	21.5−37.0%	30.4%	n/a	3.3%
Pregnant women[36, 46, 76, 77)]	Pregnant women	1.8−2.4%	0.4%	0.025%	n/a
University students[18)]	Female students without awareness of urogenital symptoms or being treated for STD	3.7%	n/a	n/a	n/a
OB-GYN medical facilities[16, 17)]	Females who visited OB-GYN medical facilities	5.9−9.6%	2.1−11.0%	n/a	n/a
PHPs[13, 19-22)]	Individuals who agreed to have tests under PHPs related to HIV and STIs (Overall)	5.0−32.8%	0.9%	1.3−2.9%	n/a
	Male subgroup	3.0−28.3%	0.6%	1.7%	n/a
	Female subgroup	8.0−39.4%	1.6%	0.5%	n/a
Testing laboratories[23-27)]	Specimens received from varied sources such as internet-accessed STI testing and medical facilities (Overall)	5.4−10.9%	1.0−8.4%	n/a	0.0−0.1%
	Male subgroup	3.4−17.4%	0.5−14.5%	n/a	0.02%
	Female subgroup	4.4−9.4%	2.0−2.2%	n/a	0.1%

n/a, not available; HIV, human immunodeficiency virus; OB-GYN, obstetrics and gynecology; PID, pelvic inflammatory disease; PHP, public health programs; STD, sexually transmitted diseases; TOA, tubo-ovarian abscess, MSM, men who have sex with men.

occurring in patients with CT and NG (7.8−36.7% for CT in NG patients[23, 28-33)] and 3.9−15.9% for NG in CT patients)[23, 29-33)]. Available gender-specific data persistently showed the trend of higher co-infection rates in female individuals than in males for all reported co-infections except for NG in CT patients (Table 2).

A total of 30.4−43.4% of CT-infected patients were revealed to be asymptomatic at diagnosis; this range tended to be higher than those of TP (27.1−40.5%) and NG (3.5−21.8%) infected patients. The gender-specific data persistently showed notably higher asymptomatic rates in female patients than in males for CT (42.6−55.4% in females vs. 3.1−6.1% in males), TP (38.3−60.5% in females vs. 21.0−36.0% in males), and NG (26.7−60.0% in females vs. 0−2.7% in males)[5, 29-33)].

The pregnancy-related outcomes included live-birth of congenital TP infections, premature birth, deformity, abortion, and still-birth. A 2015 study including 788,673 live-births, which corresponds to more than 70% of the annual deliveries in Japan, revealed an adjusted live-birth rate of 0.63 cases of confirmed congenital TP infections per 100,000 live-births[34)], which agreed with the results based on the values calculated from the NESID and the Ministry of Health, Labour and Welfare (MHLW)'s vital statistics (0.09−1.85 in 2010−2018)[5, 35)]. A study including TP-infected pregnant women reported the following pregnancy-related outcomes: premature birth (7.9%), deformity (14.5%), and still-birth (3.9%), which were significantly higher than the average rates in the general population of Japanese women, except for the premature birth rate[36)].

Table 2　Sexually transmitted co-infection rates.

Population type	Co-infected with			
	T. pallidum	*C. trachomatis*	*T. vaginalis*	*N. gonorrhoeae*
Patients with *C. trachomatis*[23, 29-33]	Overall, 0.8%; Males, 0.0%; Females, 1.0%		Overall, 0.4−1.7%; Males, 0.0%; Females, 0.6−2.3%	Overall, 3.9−15.9%; Males, 12.7−20.0%; Females, 1.0−4.0%
			Co-infected with NG and TV: Overall, 0.4%; Males, 0.0%; Females, 0.5−0.6%	
Patients with *N. gonorrhoeae*[23, 28-33]	n/a	Overall, 7.8−36.7%; Males, 7.8−37.1%; Females, 26.7−55.6%	Overall, 2.0%; Males, 0.0%; Females, 11.1%	
		Co-infected with CT and TV: Overall, 1.7−2.4%; Males, 0.0%; Females, 6.7−20.0%		
Patients with HIV[13]	35.1%	57.7%	n/a	n/a
	Co-infected with CT and TP: 27.8%			
Patients with HPV[18]	n/a	Females: 16.0%	n/a	n/a

n/a, not available; CT, *C. trachomatis*; HIV, human immunodeficiency virus; HPV, human papillomavirus; NG, *N. gonorrhoeae*; TP, *T. pallidum*; TV, *T. vaginalis*.

However, another study reported low rates of still-birth (0%) and abortion (spontaneous, induced, 0−0.0001%)[34].

A mortality rate of 0% was reported in a study including CT-infected patients diagnosed with pelvic inflammatory disease (PID) or Tubo-Ovarian Abscess (TOA)[37].

2) Treatment burden

A total of 13 studies reported the treatment burden with the following outcomes: *in vitro* susceptibility and resistance (*n*=11; 1 on CT and 10 on NG) and clinical effectiveness (*n*=3; 3 on NG).

Studies on NG reporting susceptibility and resistance evaluated various antibiotics in different classes: β-lactams, cephamycins, quinolones, tetracyclines, cephalosporins, macrolides, and aminoglycosides (Table 3). The minimum inhibitory concentration (MIC) breakout point was defined based on various references such as the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing[38, 39].

Low susceptibility and high resistance were consistently shown in different studies for β-lactams and cefmetazole. Likewise, the same trend was observed for quinolones and tetracyclines with some exceptions of low resistance ranges to minocycline and sitafloxacin (1.7−8.3% and 0.0−1.7%, respectively)[40-43]. Multi-Prefecture studies reported recent rises of resistance rates over the years for ciprofloxacin (75.7% in 2015, 76.2% in 2016 and 81.4% in 2017)[43] and for levofloxacin (70.1% in 2013, 70.8% in 2014 and 72.1% in 2015)[44].

Relatively high susceptibility and low resistance to azithromycin, spectinomycin, and ceftriaxone were reported. Two studies also reported that no NG strains were concomitantly resistant to ceftriaxone and spectinomycin or azithromycin[43, 44].

A 100% clinical effectiveness of ceftriaxone was revealed in studies including NG-positive individuals and pregnant women with gonococcal cervicitis[45, 46]. The effectiveness of azithromycin varied from 89.6% to 100% in the same types of populations[28, 46]. Additionally, a 100% clinical effectiveness of combination therapies (azithromycin with spectinomycin or with ceftriaxone) was shown in male patients with gonococcal urethritis[28].

However, a recent rise of decreased *in vitro* susceptibility to ceftriaxone over the years (MIC breakpoint of 0.12−0.25 μg/mL) was reported, with resistance rates of 3.7% in 2015,

Table 3　*In vitro* susceptibility and resistance in *N. gonorrhoeae*.

Antibiotic	Antibiotic class[A]	Susceptibility ranges	Resistance ranges	Range of study years
Ampicillin[41, 42)]	β-lactams	0.0−1.7%	34.5−83.3%	2013−2016
Azithromycin[40-45, 47, 78-80)]	Macrolides	41.9−77.4%	1.8−50.7%	2010−2017
Cefixime[40, 43-45, 47, 78, 79)]	Cephalosporins	28.9−100%	0.0−41.8%	2010−2017
Cefmetazole[42)]	Cephamycins	8.3%	91.7%	2016
Cefotaxime[41, 42)]	Cephalosporins	58.3−86.2%	41.7%	2013−2016
Cefpodoxime[40-42)]	Cephalosporins	33.3−59.2%	40.8−66.7%	2012−2016
Ceftazidime[41, 42)]	Cephalosporins	25.0−31.0%	75.0%	2013−2016
Ceftriaxone[40-45, 47, 78-80)]	Cephalosporins	68.9−100%	0.0−22.3%	2010−2017
Ciprofloxacin[40-43, 45, 47, 78-80)]	Quinolones	0.0−31.3%	68.8−100%	2010−2017
Clavulanic acid/Amoxicillin[41)]	β-lactams	0.0%	55.2%	2013
Levofloxacin[41, 42, 44)]	Quinolones	0.0−29.9%	68.5−100%	2010−2016
Minocycline[40-42)]	Tetracyclines	8.3−48.3%	1.7−8.3%	2012−2016
Penicillin G[40, 43-45, 47, 79, 80)]	β-lactams	0.0−7.7%	14.3−72.8%	2010−2017
Sitafloxacin[43)]	Quinolones	31.4−33.6%	0.0−1.7%	2015−2017
Spectinomycin[40, 43-45, 47, 80)]	Aminoglycosides	81.3−100%	0.0%	2010−2017
Tetracycline[43, 44, 47, 80)]	Tetracyclines	10.3−32.7%	1.0−74.1%	2010−2017
Tosufloxacin[41, 42)]	Quinolones	0.0−25.9%	74.1−100%	2013−2016

[A] Antibiotic classes are defined according to the Japanese Society of Chemotherapy.

4.1% in 2016, and 7.2% in 2017; another study reported the same trend over time for ceftriaxone[43, 47)]. In addition, azithromycin followed this chronologic tendency of increased *in vitro* resistance (12.1% in 2015, 16.9% in 2016, and 17.5% in 2017)[43)].

One surveillance study that aimed to assess susceptibility in CT did not identify any strains resistant to fluoroquinolone, tetracycline, or macrolide agents[15)].

3) Economic burden

Eight studies reported economic burdens with the following outcomes: hospitalization (*n*=4; 3 on CT and 1 in NG), emergency room (ER) visits (*n*=1; 1 on CT), intensive care unit (ICU) admission (*n*=1; 1 on CT), length of stay (LoS) (*n*=2; 2 on CT), surgery (*n*=2; 1 on CT and 1 on NG), and delivery-related (*n*=3; 2 on CT and 1 on TP).

Hospitalization rates were the highest in patients with serious disease conditions such as PID or Fitz-Hugh-Curtis syndrome caused by CT or NG (90.0−100%)[48, 49)]. The rates in other conditions, such as CT-positive pregnant women and genital inflammation caused by CT or NG, varied from 7.8% to 35.7%[49-51)]. A total of 60.0% of patients with Fitz-Hugh-Curtis syndrome caused by CT required ER visits, and 0.3% of hospitalized patients with PID or TOA due to CT required ICU admission[37, 48)]. The average LoS in patients with Fitz-Hugh-Curtis syndrome, PID, or TOA due to CT ranged from six to seven days[37, 48)]. Surgical interventions such as laparotomy, laparoscopic surgery, and percutaneous drainage were reported in 6.8% of patients with PID due to CT and in 26.7% with PID due to NG[37, 49)]. Operative deliveries including cesarean section, vacuum extraction, and obstetric forceps were performed in 4.2−14.4% of pregnant women with CT and 42.9% with TP[52-54)], however, one study revealed a non-significant difference in the occurrence of cesarean section and vacuum extraction between pregnant women with and without CT[52)].

4) Humanistic burden

No relevant studies were identified that evaluated the humanistic burden.

Ⅳ．Discussion

To our knowledge, this is the first study that has extensively mapped and overviewed the currently available evidence related to the epidemiological, treatment, economic, and humanistic burdens in patients infected with the four curable STIs in Japan and that has identified information gaps that require further investigation.

In 2017, an all-stage TP incidence rate of 31.4 cases per 100,000 person-years was reported in the United States (US)[55] while a rate of 7.1 was reported in Europe[56]; these rates were higher than that in data reported by the Japanese NESID (i.e., 5.5 per 100,000 person-years in 2018)[5]. However, the remarkable increase of more than 10-fold in the last 10 years was unique in Japan compared to the US and Europe. No studies have revealed the causality of this trend; however, the increased inbound flow into Japan from abroad was suggested as a hypothesis[57]. Indeed, the Japan National Tourism Organization confirms that foreign visitors to Japan continuously increased nearly four-fold from 2010 to 2018[58].

CT tended to be the most prevalent STI among the four evaluated in this review, which was aligned with the trend shown in the global estimates in the Western Pacific Region[3]. This CT-dominant trend was also observed in the STI sentinel surveillance sites monitored in the NESID program, which showed decreases in the number of notifications over the years for both CT and NG[59]. Nevertheless, there may be potential unrepresentativeness of the STI sentinel sites in the NESID due to insufficient understanding of patients' exhaustive accessibility to health facilities[10]. In fact, this review observed discrepancies between the estimated incidence of NG and CT based on the NESID sentinel surveillance data and that of exhaustive surveys, with the sentinel data of the NESID tending to report smaller incidences[10, 11].

In addition, this review demonstrated that substantial variability in the STI prevalence occurred depending on the population type. For example, patients with HIV showed the highest prevalence rates of CT and TP among different populations. The close deleterious relationship between STIs and HIV is well known[60]. A study from South Africa revealed a CT prevalence of 31.9% in HIV-positive patients attending antiretroviral clinics[61]. Additionally, 12.5% of HIV-positive patients engaged in HIV care had TP in a Canadian study[62]. Compared to these studies, our review identified higher prevalence rates of CT and TP in HIV patients. The identified studies in this review for this evidence included not only patients followed-up at medical facilities but also individuals with HIV who voluntarily participated in HIV- and STI-related PHPs organized by the Japanese municipality. Furthermore, the MSM population, which is indicated as one of the highest risk groups, was also included[63].

Repeatedly in this review, the female population was revealed to have a higher risk of co-infection and was more likely to be asymptomatic than males. Even higher asymptomatic rates of CT and NG were reported in a Canadian surveillance study, with up to 80% of the female population being asymptomatic[64]. Furthermore, a Singaporean study stated that being asymptomatic was the primary reason for not seeking STI screening[65]. In this review, only three studies targeted asymptomatic populations; most of the studies were conducted in medical facilities. Consequently, currently available evidence would not be sufficient to precisely estimate the spread of STIs in real-life in Japan and its burden in the female asymptomatic population, particularly in young women who do not have spontaneous motives to visit medical facilities. Moreover, a Japanese study showed that most cases of asymptomatic STIs are diagnosed at pregnancy checkups[33]. Among the four curable STIs, NG and TV are not currently routinely tested at pregnancy checkups with no out-of-pocket costs under public funds, contrary to CT and TP. This would further accentuate the possible underestimation, which would consequently impede the ability to assess the impact on women's reproductive lives, such as delivery-related out-

comes[66].

This review confirms that most of the studies identified assessing the treatment burden examined antimicrobial resistance (AMR) in NG. Because NG control is seriously compromised by AMR, the WHO global action plan was launched in 2012 to control the spread and impact of gonococcal AMR[67]. In Japan, the WHO global action plan was followed by the establishment of the national action plan on AMR in 2016, which strategically set multiple aims, such as the continuous monitoring of AMR and the promotion of the appropriate use of antimicrobiotics[68]. Overall, this review identified low *in vitro* resistance to and high clinical effectiveness of ceftriaxone and spectinomycin, which are recommended in the Japanese STI guidelines[4]. However, a recent rise of decreased *in vitro* susceptibility to ceftriaxone was observed in several studies. Furthermore, the first high-level ceftriaxone-resistant NG strain (H041) was isolated in Japan in 2009[69]. Nevertheless, this review identified only two nationwide recurrent AMR surveillance schemes for NG; these surveys were both conducted generally at two- to three-year intervals. The scale and frequency of those surveys were reduced compared to the US Gonococcal Isolate Surveillance Project, in which NG specimens are continuously collected each month from the selected sentinel sites[70].

There was a scarcity of studies providing evidence regarding the economic burden in this review. A US study that included adolescents and young adults assessed direct medical costs of incident infections for three STIs (CT, NG, and TP). They reported costs of approximately 30 million USD per year and clarified the importance of assessing the economic burden to maximize effectiveness in preventive efforts and reducing costs[71]. No evidence was identified that assessed the humanistic burden; in fact, this lack of evidence was also stated in a systematic review performed in global settings[72].

Scarcity was also revealed for evidence related to the population of commercial sex workers (CSWs). Although the CSW population is consistently identified as one of the most vulnerable populations for the spread of STIs[73], this review did not identify any studies that focused on CSWs. The total number of female CSWs in Japan was conservatively estimated at approximately 325,000−390,000 based on the estimated number of legal and illegal CSW bases[74]. Despite a deep-rooted taboo conscience and non-reactivity vis a vis this population in the Japanese governmental body[75], this estimated number raises imminent awareness to public entities of the importance of understanding the entire picture of the STI burden in the CSW population.

Although this study presents evidence based on an extensive review performed according to a defined process, the results should be cautiously interpreted due to the limitation that studies regarding diseases caused by STIs without explicitly mentioning the target four curable STIs might not have been captured by our search strategy. However, the search strategy employed search terms that enabled us to search in broad fields including the term “thesaurus.” Therefore, the identified studies were assumed to be reliable and valid for achieving the study objectives.

Ⅴ. Conclusion

In conclusion, this review identified that more abundant data were available on the epidemiological and treatment burdens in CT and NG. However, the overall evidence underscores the importance of further considering variability in patients’ characteristics such as vulnerability, treatment accessibility, and asymptomatic rates, enhancement of AMR surveillance systems, and fulfilment of research gaps due to data scarcity. Valid evidence generated from pertinent studies is indispensable to conceptualize, plan, implement, and evaluate measures and preventive educational programs, which will finally lead us to break the chain of infection.

Conflicts of Interest

The authors declare no conflicts of interest.

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Ethical concerns

Ethical concerns are unnecessary since only published data sources were used in this study.

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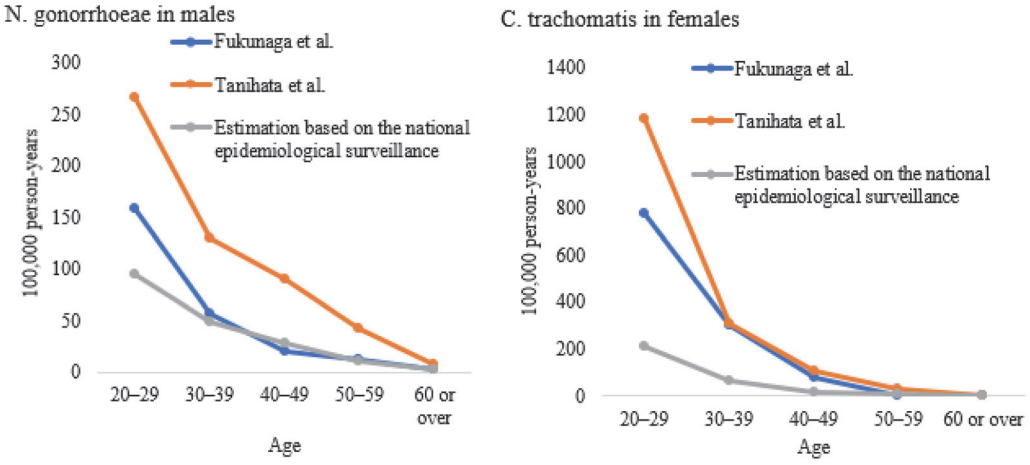
List of Abbreviations

AMR	AntiMicrobial Resistance
CLSI	Clinical and Laboratory Standards Institute
CSWs	Commercial Sex Workers
CT	*Chlamydia trachomatis*
DALY	Disability-Adjusted Life Year
ER	Emergency Room
HIV	Human Immunodeficiency Viruses
HPV	Human PapillomaVirus
HRQoL	Health-Related Quality of Life
ICHUSHI	Igaku Chuo Zasshi
ICU	Intensive Care Unit
LoS	Length of Stay
MHLW	Ministry of Health, Labour and Welfare
MIC	Minimum Inhibitory Concentration
MSM	Men who have Sex with Men
NESID	National Epidemiological Surveillance of Infectious Diseases
NG	*Neisseria gonorrhoeae*
NIID	National Institute of Infectious Diseases
OB-GYN	OBstetrics and GYNecology
PHPs	Public Health Programs
PID	Pelvic Inflammatory Disease
PK	PharmacoKinetics
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
SLR	Systematic Literature Review
STIs	Sexually Transmitted Infections
STD	Sexually Transmitted Diseases
TOA	Tubo-Ovarian Abscess
TP	*Treponema pallidum* subspecies *pallidum*
TV	*Trichomonas vaginalis*
US	United States
WHO	World Health Organization

Appendix 1　Study scope applied to the literature review (PICOS inclusion and exclusion criteria).

	Inclusion criteria	Exclusion criteria
Population	Patients with at least one of the curable STIs of interest (*C. trachomatis, N. gonorrhoeae, T. pallidum, T. vaginalis*). All genders. All severity levels. Adolescents or older.	None
Intervention	Any	n/a
Comparator	Any	n/a
Outcomes	Epidemiological burden (Incidence; prevalence; morbidity; mortality; risk factor; progression; evolution; development; sequelae; unmet needs)	None
	Treatment burden (Treatment regimen; effectiveness; treatment failure; susceptibility; resistance)	
	Humanistic burden (QoL; HRQoL; DALY; QALY; utility; disutility; disability; functional status; physical function)	
	Economic burden (Cost of illness; resource use; healthcare use; hospitalization; length of stay; productivity loss (sick day, work disability, work impairment); willingness to pay; cost-effectiveness; caregiver costs)	
Study design	Observational studies, database analyses, economic evaluations	Not the study type of interest (e.g. review[A], SLR[A], letter, commentary, notes, opinions, case reports, PK studies, Clinical trials)
Others	Geographical scope: Japan	Study setting: Single-facility studies and studies with small effect size (i.e. less than *N*=50) for epidemiological and treatment outcomes
	Language: English or Japanese	
	Timeframe: From 2010 onward for epidemiological and treatment outcomes	

[A] Review and SLR articles were excluded after references were checked during full-text screening.
n/a: not applicable; DALY: Disability-Adjusted Life Year; HRQoL: Health-Related Quality of Life; PK: Pharmacokinetics; QALY: Quality-Adjusted Life Year; QoL: Quality of Life; SLR: Systematic Literature Review.



Appendix 2　Incidence rates of *N. gonorrhoeae* in males and *C. trachomatis* in females by age group.
References: Fukunaga et al.[11], Tanihata et al.[10], estimation based on the national epidemiological surveillance[10].

日本における4種の治療可能な性感染症の疾病負荷とエビデンスギャップ：系統的文献レビュー

福島　彩子　　池田　俊也

抄　録

目的：系統的文献レビューで，4種のSTIにおける日本での疾病負荷研究をマッピングし，エビデンスギャップの特定を目的とした．

方法：青年期以上の対象性感染症をもつ患者を対象にPubMedと医中誌で検索を行った．アウトカムには，疫学，治療，経済的，および人道的負荷が含まれた．

結果：疫学（$n = 31$），治療（$n = 13$），および経済的負荷（$n = 8$）を報告する48件の文献が特定された．人道的負荷に関する研究は特定されなかった．最も研究された性感染症としては，クラミジア（$n = 28$）と淋病（$n = 27$）であった．全国的サーベイランスにおける定点調査においてクラミジアと淋病が継続的に減少していることが示された．ただし，調査定点の非代表性も示唆された．有病率，重複感染，および無症候性の発生率に関する報告では，併存疾患や性別等の人口特性に依存し，幅広い発生率が明らかになった．経済的および人道的負荷とセックスワーカーに関するデータは希少であった．

考察：本研究は，患者の脆弱性，治療へのアクセス，無症候性等の患者特性の考慮，抗菌薬耐性監視の強化，データ不足を補足するさらなる研究の必要性を示した．

キーワード：疾病負荷研究，性感染症，系統的文献レビュー