

Worldwide Susceptibility Rates of *Neisseria gonorrhoeae* Isolates to Cefixime and Cefpodoxime: A Systematic Review and Meta-Analysis

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Abstract

Background: *Neisseria gonorrhoeae* (NG) infection is a serious public health problem. The third-generation extended-spectrum cephalosporins (ESCs) have been used as the first-line treatment for NG infection for almost three decades. However, in recent years, treatment failures with the oral third-generation ESCs have been reported worldwide. This study aimed to estimate worldwide susceptibility rates of NG to cefixime and cefpodoxime by analyzing data from all relevant published studies.

Methodology/principal findings: Two researchers independently searched five databases to identify studies on susceptibilities of NG to cefixime and cefpodoxime published between January 1, 1984 and October 15, 2012. A fixed-effect model was used to perform group analysis, and a χ^2 test was employed to make subgroup comparison. Publication bias was assessed with the Begg rank correlation test. The pooled susceptibility rate of NG isolates to cefixime was 99.8% (95% CI: 99.7%–99.8%). The cefixime susceptibility rate of NG isolates from men was significantly lower than that from patients without information of gender or from men and women; the susceptibility rate of NG isolates from Asia was significantly lower than that from other continents; and the susceptibility rate of NG isolates collected before or during 2003 was significantly higher than that after 2003. The pooled susceptibility rate of NG isolates to cefpodoxime was 92.8% (95% CI: 89.0%–95.3%), which was lower than that to cefixime (92.8% vs. 99.8%, $\chi^2 = 951.809$, $P < 0.01$).

Conclusions: The susceptibility rate of NG isolates to cefixime varied with the gender of patients and geographical location from which NG isolates were collected, and declined with time. The reported lower susceptibility rate of NG isolates to cefixime and associated treatment failures, as well as the emergence of NG strains with cephalosporin resistance call for the more effective control of NG infection and the development of new antibiotics.

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Introduction

Neisseria gonorrhoeae (NG) is a common sexually transmitted pathogen which causes male urethritis and female endocervicitis. The World Health Organization (WHO) estimated that there were 106 million new cases of gonorrhea worldwide in 2008 [1]. During the past three decades, NG has developed resistance to most of the antibiotics used to treat gonorrhea, including penicillin, tetracyclines, and fluoroquinolones [2,3,4]. In the 1990s, the third-generation extended-spectrum cephalosporins (ESCs) were recommended internationally to treat NG infection [5]. However, during the past two decades, there have been reports on verified treatment failures with cefixime in Japan, France, Norway, Austria, United Kingdom, and Canada; with ceftriaxone in Sweden and Australia; with cefibuten in Hong

Kong; and with cefdinir in Japan [6,7,8,9,10,11,12,13,14,15,16]. As a result, the oral ESCs are not currently recommended for treating NG infection in Japan, urban areas of Australia, Europe, and United States [17,18,19,20]. However, cefixime is still the recommended drug for NG infection in Canada [21]. According to the Clinical and Laboratory Standards Institute (CLSI), the minimum inhibitory concentration (MIC) breakpoint for oral ESCs cefixime and cefpodoxime susceptibility were <0.25 mg/L and 0.5 mg/L respectively [22]. To date, there have been many studies on antimicrobial susceptibilities of NG to cefixime and cefpodoxime. The aim of this study were: (1) to estimate the susceptibility rates of NG to cefixime and cefpodoxime worldwide from relevant studies; (2) to compare cefixime susceptibility rate of NG isolates collected from different populations and locations, and its development over time.

Table 1. Overview of 25 included studies on cefixime and cefpodoxime susceptibility rates of NG isolates.

| Study number | First author, year | Location | Isolate collection period ^a | Population ^b | Drug | No. isolates | Susceptibility rate(%) ^c |
|--------------|------------------------|---------------------------------|--|-------------------------|-------------|--------------|-------------------------------------|
| 1 | Fekete T, 1991 [50] | Philadelphia and San Diego, USA | - | Mix | Cefpodoxime | 77 | 100 |
| 2 | Kohl PK, 1995 [41] | Heidelberg, Germany | 1986–1990 | Mix | Cefixime | 203 | 100 |
| 3 | Lewis DA, 1995 [42] | East London, England | - | Patients | Cefixime | 104 | 100 |
| 4 | Tapsall JW, 1995 [51] | Sydney, Australia | 09/1993–12/1993 | Mix | Cefpodoxime | 137 | 100 |
| 5 | Lewis DA, 1996 [34] | London, England | 04/1992–03/1993 | Patients | Cefixime | 378 | 100 |
| 6 | Nissinen A, 1997 [35] | Finland | 1993 | Mix | Cefixime | 337 | 98 |
| 7 | Fox KK, 1997 [39] | Surveillance sites, USA | 1992 and 1994 | Patients | Cefixime | 10402 | 99.856 |
| | | | 1992 | Patients | Cefixime | 5406 | 99.8 |
| | | | 1994 | Patients | Cefixime | 4996 | 99.92 |
| 8 | Komeda H, 2004 [47] | Ogaki, Japan | 1998–2002 | Men | Cefpodoxime | 147 | 88.8 |
| | | | 1998 | Men | Cefpodoxime | 28 | 93.3 |
| | | | 1999 | Men | Cefpodoxime | 30 | 96.8 |
| | | | 2000 | Men | Cefpodoxime | 30 | 88.2 |
| | | | 2001 | Men | Cefpodoxime | 30 | 82.9 |
| 2002 | Men | Cefpodoxime | 29 | 89.1 | | | |
| 9 | Shigemura K, 2004 [44] | Hyogo and Osaka, Japan | 2004 | Men | Cefixime | 87 | 100 |
| 10 | Kagami Y, 2005 [40] | Tokyo, Japan | 1999–2004 | Men | Cefixime | 281 | 95.7 |
| | | | 1999 | Men | Cefixime | 41 | 100 |
| | | | 2000 | Men | Cefixime | 57 | 93 |
| | | | 2001 | Men | Cefixime | 24 | 100 |
| | | | 2003 | Men | Cefixime | 58 | 96.6 |
| 2004 | Men | Cefixime | 101 | 94.1 | | | |
| 11 | Donegan EA, 2006 [27] | Bali, Indonesia | 08/2004–11/2005 | FSWs | Cefixime | 147 | 100 |
| | | | | FSWs | Cefpodoxime | | 100 |
| 12 | Zarakolu P, 2006 [46] | Turkey, Ankara | - | Sex workers | Cefixime | 30 | 100 |
| 13 | De Jongh, 2007 [30] | Pretoria | 03/2004–04/2005 | Men | Cefpodoxime | 141 | 100 |
| 14 | Wang S, 2007 [35] | USA | 1992–2003 | Mix | Cefixime | 62461 | 99.928 |
| 15 | Palmer HM, 2008 [48] | Scottish | 04/2004–03/2006 | Mix | Cefixime | 1765 | 100 |
| 16 | Apalata T, 2009 [38] | Maputo, Mozambique | 03/2005–04/2005 | Patients | Cefixime | 55 | 100 |
| 17 | Allen VG, 2011 [31] | Ontario, Canada | 10/2008–11/2008 | Patients | Cefixime | 149 | 100 |
| 18 | Endo K, 2011 [28] | Tokyo, Japan | 2006–2010 | Men | Cefixime | 156 | 86.5 |
| | | | 2006 | Men | Cefixime | 47 | 100 |
| | | | 2007 | Men | Cefixime | 23 | 100 |
| | | | 2008 | Men | Cefixime | 18 | 100 |
| | | | 2009 | Men | Cefixime | 38 | 47.4 (outlier) |
| 2010 | Men | Cefixime | 30 | 96.7 | | | |
| 19 | Lee H, 2011 [33] | Korea | 2001–2006 | Mix | Cefixime | 162 | 99.38 |
| | | | 2001 | Mix | Cefixime | 41 | 100 |
| | | | 2002 | Mix | Cefixime | 25 | 100 |
| | | | 2003 | Mix | Cefixime | 24 | 100 |
| | | | 2004 | Mix | Cefixime | 20 | 95.8 |
| | | | 2005 | Mix | Cefixime | 21 | 100 |
| 2006 | Mix | Cefixime | 31 | 100 | | | |
| 20 | Martin I, 2011 [43] | Canada | 2000–2009 | Mix | Cefixime | 10993 | 99.45 |
| 20 | Martin I, 2011 [43] | | 2000 | Mix | Cefixime | 1206 | 100 |
| | | | 2001 | Mix | Cefixime | 1234 | 100 |
| | | | 2002 | Mix | Cefixime | 1163 | 100 |
| | | | 2003 | Mix | Cefixime | 800 | 100 |

Table 1. Cont.

| Study number | First author, year | Location | Isolate collection period ^a | Population ^b | Drug | No. isolates | Susceptibility rate(%) ^c |
|--------------|-------------------------|-------------------------------------|--|-------------------------|----------|--------------|-------------------------------------|
| | | | 2004 | Mix | Cefixime | 855 | 100 |
| | | | 2005 | Mix | Cefixime | 905 | 100 |
| | | | 2006 | Mix | Cefixime | 1532 | 100 |
| | | | 2007 | Mix | Cefixime | 1438 | 99.93 |
| | | | 2008 | Mix | Cefixime | 947 | 99.894 |
| | | | 2009 | Mix | Cefixime | 913 | 99.56 |
| 21 | Tanaka M, 2011 [49] | Western, Mid-eastern, Eastern Japan | 02/2008–12/2009 | Mix | Cefixime | 494 | 99.6 |
| 22 | Tanaka M, 2011 [29] | Fukuoka, Japan | 01/2008–12/2008 | Patients | Cefixime | 242 | 98.76 |
| 23 | Carannante A, 2012 [32] | Italy | 2006–2010 | Men | Cefixime | 293 | 99.32 |
| 24 | Mehta S, 2012 [36] | Kisumu, Kenya | 2002–2009 | Young men | Cefixime | 168 | 100 |
| 25 | Takahashi S, 2012 [45] | Sapporo, Japan | 01/2007–01/2009 | Men | Cefixime | 51 | 92.2 |

^aIsolate collection period: “-” means this information unavailable.

^bStudy population: FSWs (female sex workers); men (men with urethritis); mix (male and female patients), patients (patients whose gender was not identified); young men (young men with discharge); Sex workers (sex workers whose gender was not identified).

^cSusceptibility rate = number of susceptible NG isolates/total number of isolates tested × 100.

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Methods

Literature search

Two independent researchers (RY and GW) searched five databases (PubMed, Embase, Web of Science, CNKI, and Wanfang) to identify relevant studies published from August 1984 to October 2012. Search terms included “*Neisseria gonorrhoeae*,” “*gonorrhoea*,” or “*gonococcus*”; and their combinations with “*cefixime*” or “*cefpodoxime*,” and with subject headings “*MIC*,” “*minimum inhibitory concentration*,” “*resistance*,” “*resistant*,” “*susceptible*,” or “*susceptibility*.” (See Table S1) References cited in the retrieved articles were also screened, and duplicated reports were excluded. This review was conducted in four stages (identification, screening, eligibility assessment, and inclusion) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23,24]. (See Table S2)

Eligibility criteria and validity assessment

The included studies met the following criteria: (1) original studies published between January 1, 1984 and October 15, 2012 in any language; (2) specified the total number of NG isolates; (3) determined the MICs of cefixime or cefpodoxime with agar dilution method; and (4) following CLSI standards, reported the antimicrobial susceptibility rate in NG isolates, or implied it by indicating their MICs of cefixime or cefpodoxime, and/or the number of non-susceptible NG isolates. According to the above criteria, the eligibility and validity of selected studies were assessed independently by two researchers (RY and GW), any disagreement was resolved by involving the third researcher (YY).

Data extraction

Data was extracted from each included study and compiled under the following categories using a standardized form: (1) first author and publication year; (2) location (country and city) where the study was conducted; (3) isolates collection period; (4) study population, if available; (5) drugs: cefixime and/or cefpodoxime; (6) number of tested isolates; and (7) susceptibility rate (**Table 1**). The data was extracted independently by two authors (RY and

GW), any resultant discrepancies were resolved by involving the third researcher (YY).

Quality assessment

A set of criteria including location, isolates collection period, population, isolates identification, NO. of the isolates, NO. of NG isolates ≥ 100 , and control strains these seven factors (Table 2), was used for assessing quality of the included studies. The quality assessment was independently performed by two researchers (RY and GW), and any resultant discrepancies were resolved by involving the third researcher (YY).

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences for Windows (SPSS, version 20.0, Chicago, IL, USA), MetaAnalyst Beta 3.13 software, and Stata 12.0 software. The antimicrobial susceptibility rate in NG isolates with corresponding 95% confidence intervals (CI) was calculated for each individual study. A fixed-effects model was used to perform group analysis. Based on NG isolates collected from different populations and continents in the included studies, a fixed subgroup analysis was used and a χ^2 test was employed to make subgroup comparison ($P < 0.05$ indicating statistical significance). Furthermore, because the first case of treatment failure with cefixime was reported in 2003 [6], we divided NG isolates into two groups— isolates collected before or during 2003 and those after 2003. Between-study heterogeneity was measured by performing the Q test ($P < 0.10$ indicating statistical significance) and calculating I^2 values (ranging between 0% and 100%, with lower values representing less heterogeneity) [25]. Publication bias was assessed using the Begg rank correlation test ($P < 0.05$ indicating statistical significance) [26].

Results

Study selection

A total of 744 potential abstracts were identified, of which 231 were duplicate records and were thus removed (Figure 1). All of the remaining 513 abstracts were screened, of which 417 were

Table 2. Quality assessment of the studies included in meta-analysis.

| Study number | First author, year | Location ^a | Isolates collection period ^b | Population ^c | Isolates identification ^d | NO. isolates ^e | NO. of NG isolates \geq 100 ^f | Control strains ^g |
|--------------|--------------------|-----------------------|---|-------------------------|--------------------------------------|---------------------------|--|------------------------------|
| 1 | Fekete T, 1991 | + | – | + | + | + | – | – |
| 2 | Kohl PK, 1995 | + | + | – | + | + | + | – |
| 3 | Lewis DA, 1995 | + | – | – | + | + | + | + |
| 4 | Tapsall JW, 1995 | + | + | – | – | + | + | – |
| 5 | Lewis DA, 1996 | + | + | – | + | + | + | + |
| 6 | Nissinen A, 1997 | + | + | + | + | + | + | – |
| 7 | Fox KK, 1997 | + | + | – | – | + | + | + |
| 8 | Komeda H, 2004 | + | + | + | – | + | + | – |
| 9 | Shigemura K, 2004 | + | + | + | – | + | – | + |
| 10 | Kagami Y, 2005 | + | + | + | – | + | + | – |
| 11 | Donegan EA, 2006 | + | + | + | + | + | + | + |
| 12 | Zarakolu P, 2006 | + | – | + | + | + | – | + |
| 13 | De Jongh, 2007 | + | + | + | + | + | + | + |
| 14 | Wang S, 2007 | + | + | + | – | + | + | + |
| 15 | Palmer HM, 2008 | + | + | – | – | + | + | – |
| 16 | Apalata T, 2009 | + | + | – | + | + | – | + |
| 17 | Tanaka M, 2011 | + | + | + | + | + | + | + |
| 18 | Martin I, 2011 | + | + | – | – | + | + | + |
| 19 | Lee H, 2011 | + | + | + | – | + | + | + |
| 20 | Endo K, 2011 | + | + | + | + | + | + | + |
| 21 | Tanaka M, 2011 | + | + | – | – | + | + | – |
| 22 | Allen VG, 2011 | + | + | – | + | + | + | + |
| 23 | Carannante A, 2012 | + | + | + | – | + | + | + |
| 24 | Takahashi S, 2012 | + | – | + | + | + | – | + |
| 25 | Mehta S, 2012 | + | + | + | + | + | + | – |

^a“+” means the study specifying the location where NG isolates were collected; “–” stands for this information missing from the study.

^b“+” means the study specifying isolates collection period; “–” stands for this information missing from the study.

^c“+” means the study describing the population from whom NG isolates were obtained; “–” stands for this information missing from the study.

^d“+” means the study describing the method of identifying NG isolates; “–” stands for this information missing from the study.

^e“+” means the study indicating the number of tested NG isolates; “–” stands for this information missing from the study.

^f“+” means the study including at least 100 tested NG isolates; “–” stands for the study failing to do it.

^g“+” means the study utilizing control strains recommended by WHO in determining MICs with agar dilution method; “–” stands for the study failing to do it.

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found to have no data concerning cefixime and cefpodoxime susceptibilities and were thus excluded. Therefore, a total of 96 full-text articles were assessed for eligibility; 25 of them were included in the meta-analysis, comprising 21 on antimicrobial susceptibility rate to cefixime and five to cefpodoxime. Of all the included studies, only two studies included the data on susceptibility rates of NG isolates collected after 2010. (Table 1).

Quality assessment

Among the 25 included studies, only four [27,28,29,30] reported all seven of the categories in our data matrix, seven [31,32,33,34,35,36,37] reported data on six of these categories, ten [38,39,40,41,42,43,44,45,46,47] provided information on five of these categories, and four [48,49,50,51] reported data of only four of these categories (Table 2). The quality of an included study was negatively scored in particular when it failed to describe the study population or NG isolate identification method. Additionally, studies that did not use control strains recommended by the WHO in determining MICs were also scored negatively with respect to quality.

Meta-analysis

Susceptibility rate of NG to cefixime. By performing a meta-analysis with fixed model, the pooled susceptibility rate of NG isolates to cefixime was found to be 99.8% (95%CI: 99.7%–99.8%), and evidence of moderate heterogeneity ($I^2 = 48.1\%$, $P < 0.001$) was observed between included studies (Figure 2). Moreover, significant publication bias was detected (Begg rank correlation test, $P = 0.007$). In the included 21 studies on cefixime [27,28,29,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,48,49], the susceptibility rate of NG isolates to the antibiotic ranged from 92.2% to 100%, with the median of 99.5%. The susceptibility rate was $\geq 95\%$ in all studies except one conducted in Japan. It reported a susceptibility rate of 92.2% (95% CI: 20.9%–97.0%). Furthermore, non-susceptible isolates were collected from men and the collection period was from January 2007 to January 2009 [45]. In another study conducted in Japan, the susceptibility rate were 99.1% (95%CI: 93.9%–99.9%) after an abnormally low susceptibility rate of 47.4% in 2009 was omitted from the analysis [28].

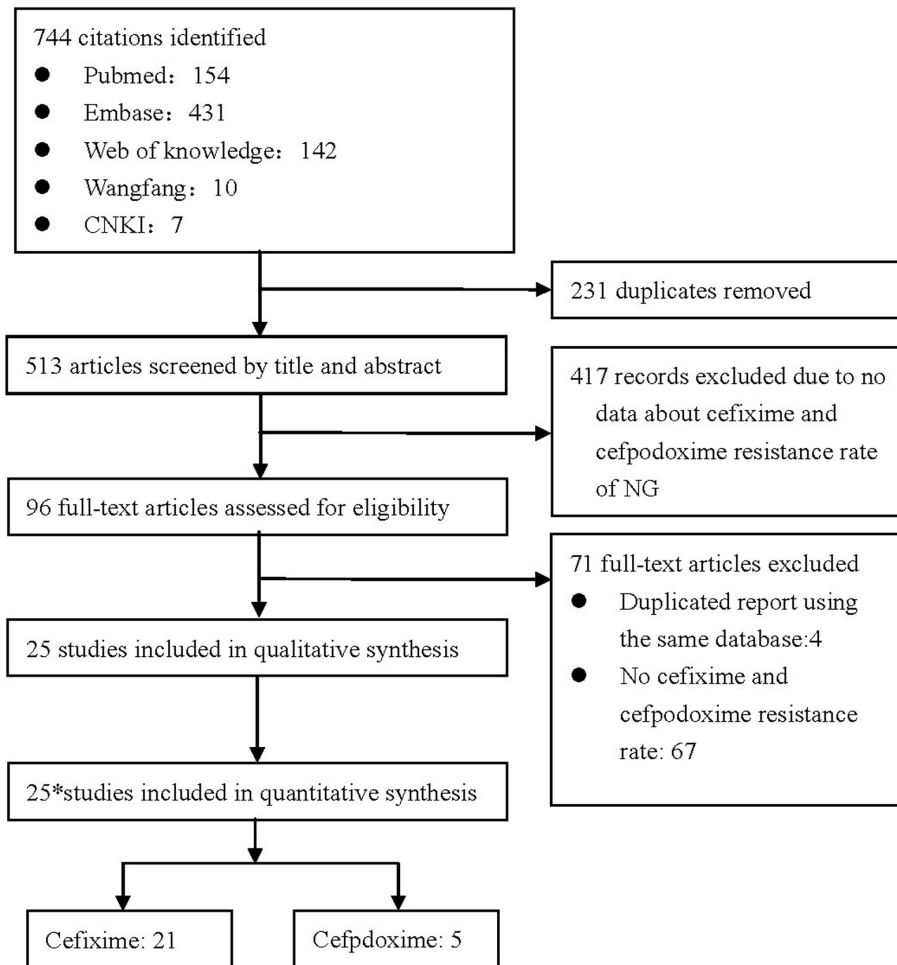


Figure 1. Process of selecting published studies for the meta-analysis according to PRISMA guidelines. * One of the 25 studies contains data concerning both cefixime and cefpodoxime. doi:10.1371/journal.pone.0087849.g001

Comparison of cefixime susceptibility rates between included studies. As shown in Table 3, performing a subgroup meta-analysis reduced the heterogeneity of this review. The susceptibility rate of NG isolates from men was lower than that from patients without information on gender or mixed gender group (men and women) (96.5% vs. 99.8%, $\chi^2 = 1341.499$, $P < 0.001$; 96.5% vs. 99.9%, $\chi^2 = 6776.778$, $P < 0.001$). There was a statistically significant difference in the cefixime susceptibility rates between different continents ($\chi^2 = 692.379$, $p < 0.001$); and this rate was lower in Asia than in Europe (97.4% vs. 99.0%, $\chi^2 = 669.637$, $P < 0.001$) and North America (97.4% vs. 99.9%, $\chi^2 = 183.740$, $P < 0.001$), or Africa (97.4% vs. 99.5%, $\chi^2 = 3.987$, $P = 0.046$). Cefixime susceptibility rate of NG isolates was lower in Japan than in other Asian countries (93.8% vs. 99.3%, $\chi^2 = 6.069$, $P = 0.014$). The NG isolates collected before or during 2003 were more susceptible than those collected after 2003 (99.8% vs. 99.0%, $\chi^2 = 198.597$, $P < 0.001$).

Distribution of NG isolates with MIC > 0.25 mg/L for cefixime. A total of 118 NG isolates with a MIC of > 0.25 mg/L for cefixime were identified in 11 studies [28,29,32,35,37,39,40,43,45,49]. The highest number of non-susceptible isolates was found in the United States ($n = 60$), followed by Japan ($n = 42$), while substantially lower numbers of

such isolates were identified in Finland ($n = 7$), Canada ($n = 6$), Italy ($n = 2$), Korea ($n = 1$).

Susceptibility rate of NG isolates to cefpodoxime. Analyzing all the included studies on cefpodoxime susceptibility rates of NG isolates, the pooled susceptibility rate of NG isolates to cefpodoxime was 92.8% (95% CI: 89.0%–95.3%) and evidence for between-study heterogeneity ($I^2 = 44.6\%$, $P < 0.001$) was observed. No significant publication bias was found (the Begg rank correlation test, $P = 0.197$). The susceptibility rate of NG isolates to cefpodoxime was lower than that to cefixime (92.8% vs. 99.8%, $\chi^2 = 951.809$, $P < 0.001$); the former ranged from 89.9% (95% CI: 84.5%–93.5%) to 100% (95% CI: 95.6%–100%) over the five included studies concerning cefpodoxime susceptibility (Figure 3) [27,30,47,50,51]. Four reported cefpodoxime susceptibility rates of 100%, and one documented a rate of 89.9%. Isolates for this study were collected from men between 1998 and 2002.

Discussion

Cefixime and cefpodoxime are orally administered antimicrobials, with a spectrum of activity against bacterial infections similar to that of ceftriaxone [52]. Although data from previously published studies indicate that NG was generally susceptible to

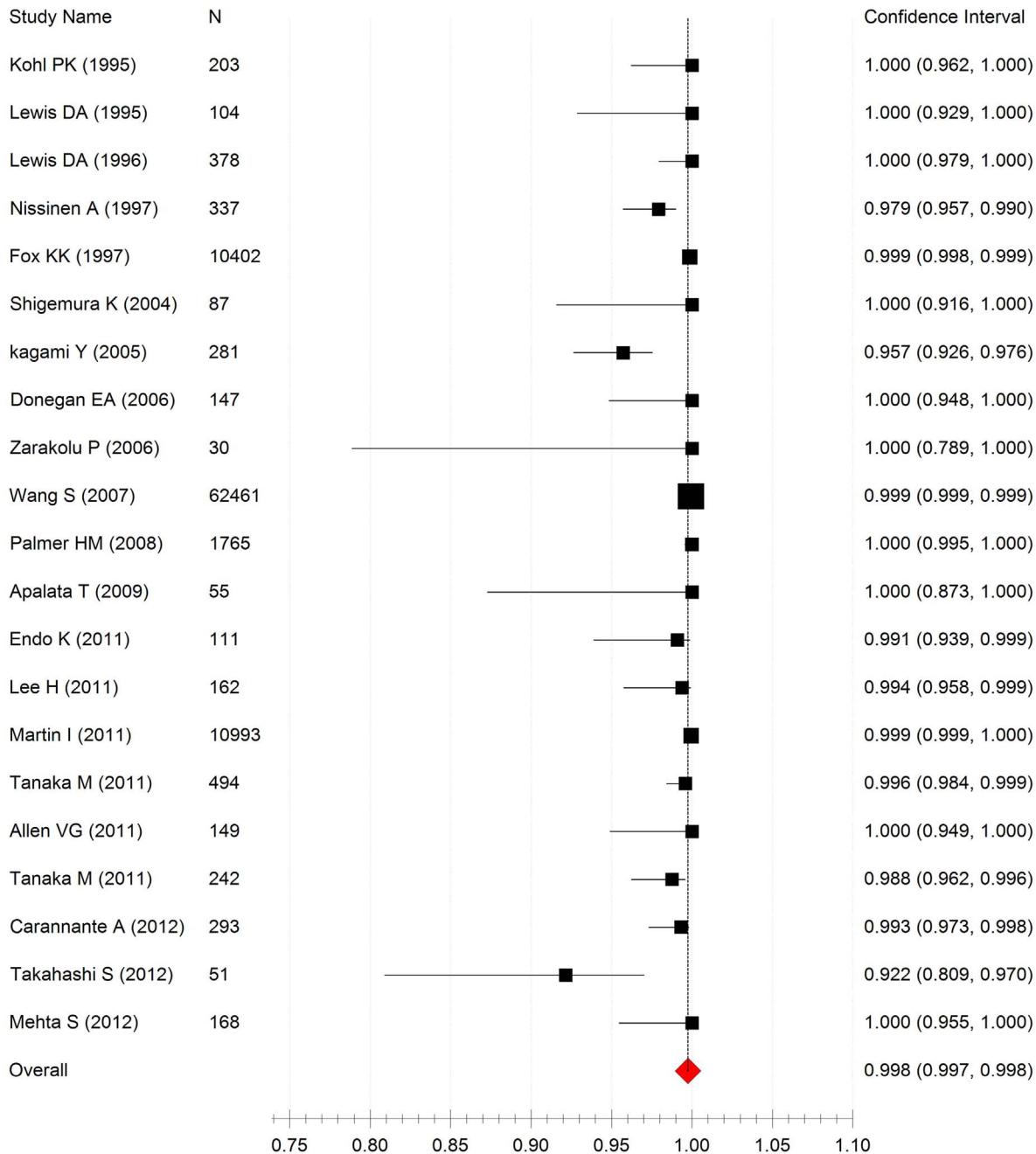


Figure 2. Forest plot of cefixime susceptibility rates in NG isolates from 21 included studies. Heterogeneity ($I^2 = 48.1\%$, $P < 0.001$). doi:10.1371/journal.pone.0087849.g002

cefixime, evidence from the most current surveillance programs is needed to guide clinical practice. Global and national programs have been developed to improve monitoring of gonococcal resistance, such as the WHO Gonorrhoea Antimicrobial Surveillance Programme (GASP) in Asia and Pacific [17], Australian Gonococcal Surveillance Programme (AGSP) in Australia [18], the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) in England and Wales [19] and the Gonococcal Isolate Surveillance Project (GISP) [20] in US. Based on the results from these programs, cefixime has been excluded as a first line drug for treating NG infection in Japan, urban areas of Australia, Europe, and United States. Ongoing use of cefixime may increase the chance of NG developing resistance towards the currently

most reliable gonorrhoea treatment drug ceftriaxone, which is mediated by the same mosaic Penicillin-Binding Protein 2 (PBP2) [53]. Such increased selective pressure for resistance in gonococci to ceftriaxone may be even more obvious in some specific populations and locations where antibiotics may be widely used (or even misused) in medical practice [54].

In this review, we report that cefixime susceptibility rate of NG isolates from men was lower than that from patients whose gender was not identified, or that from men and women. Consistently, in the past few years, all patients treated unsuccessfully with cefixime were found to be men except one women in one study reported by Allen et al. [6,7,8,9,10,15,16], suggesting that men including men who have sex with men (MSM) are at higher risk of pharyngeal

Table 3. Subgroup analysis for cefixime susceptibility rates.

| Subgroup type | Susceptibility rate (95%CI) | No. of the NG isolates | No. of the studies | Heterogeneity | | χ^2 test | |
|---------------------------------|-----------------------------|------------------------|--------------------|--------------------|------------------|---------------|----------|
| | | | | I ² (%) | P-value | χ^2 | P-value |
| Population^a | | | | | | | |
| Men (RS) | 96.5 (94.6–97.8) | 868 | 5 | 0.405 | <0.001 | - | - |
| mix | 99.9 (99.9–99.9) | 76415 | 7 | 0.480 | <0.001 | 1341.499 | <0.001 |
| Patients | 99.8 (99.7–99.9) | 11330 | 6 | 0.383 | 0.022 | 6776.778 | <0.001 |
| FSWs | 99.7 (94.8–100.0) | 147 | 1 | - | - | - | - |
| Sex workers | 98.4 (78.9–99.9) | 30 | 1 | - | - | - | - |
| Young men | 99.7 (98.3–99.8) | 168 | 1 | - | - | - | - |
| Continents | | | | | | | |
| Asia (RS) | 97.4 (95.7–98.1) | 1650 | 9 | 0.397 | <0.001 | - | - |
| Europe | 99.0 (98.1–99.4) | 3080 | 6 | 0.389 | 0.017 | 669.637 | <0.001 |
| North America | 99.9 (99.9–99.9) | 84005 | 4 | 0.375 | 0.054 | 183.740 | <0.001 |
| Africa | 99.5 (96.4–99.9) | 223 | 2 | <0.001 | 0.367 | 3.987 | 0.046 |
| Japan or other countries | | | | | | | |
| Other Asian countries (RS) | 99.3 (97.3–99.8) | 339 | 3 | <0.001 | 0.416 | - | - |
| Japan | 93.8 (91.6–95.4) | 1311 | 6 | 0.468 | <0.001 | 6.069 | 0.014 |
| Other continents | 99.9 (99.8–99.9) | 87366 | 12 | 0.466 | <0.001 | 3.768 | 0.052 |
| Collection period | | | | | | | |
| Before or during 2003 (RS) | 99.8 (99.8–99.9) | 78558 | 9 | 0.485 | <0.001 | - | - |
| After 2003 | 99.0 (98.6–99.3) | 10202 | 13 | 0.460 | <0.001 | 198.597 | <0.001 |
| Unknown | 99.3 (95.3–99.9) | 198 | 2 | <0.001 | 0.283 | - | - |
| Overall | 99.8 (99.7–99.8) | 88958 | 21 | 0.481 | <0.001 | - | - |

^aStudy population: FSWs (female sex workers); men (men with urethritis); mix (male and female patients), patients (patients whose gender was not identified); young men (young men with discharge); Sex workers (sex workers whose gender was not identified). RS: Reference Subgroup (the subgroups compared with others by χ^2 test).

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NG infections, which are difficult to treat and where resistant strains are more like to develop [55,56]. Therefore, it is important to monitor antimicrobial susceptibilities in patients, in particular male patients, to guide gonorrhea antimicrobials treatment, and to better control gonorrhea.

To the best of our knowledge, no prior study has compared cefixime susceptibility rates of NG isolates among different continents. The present study revealed significant differences in susceptibility rate among different continents. Specifically, the cefixime susceptibility rate in Asia was lower than that in other continents, and was particularly low in Japan as compared to other Asian countries. This indicates that NG isolates from Japan were less susceptible to cefixime relative to those from other countries. However, cefixime susceptibility rates in Asia have only been reported in four countries (Japan, Korea, Indonesia, and Turkey), but not in China and India, the two most densely populated countries in the world.

In the included studies, the cefixime susceptibility rate of NG isolates did not appear to significantly change along with the time period (Figure 2). However, the cefixime susceptibility rate in NG isolates collected before or during 2003 was significantly higher than that in isolates collected after 2003, suggesting that worldwide cefixime susceptibility rates in NG isolates has significantly decreased since 2003. Additionally, a decrease in cefixime susceptibility has been noted in certain countries, including Hawaii, Japan, Canada, and Sweden [29,31,57,58]. Although at present NG is still generally susceptible to cefixime worldwide, the

susceptibility may decrease with time as the incidence of non-susceptible isolates keeps rising. Furthermore, several studies reported that NG showed a decreased susceptibility to ceftriaxone [31,45,59,60,61,62]. Thus, it is necessary to develop a wider range of antimicrobial options for super resistant NG strains that are resistant to ESCs as well as other antibiotics [15,53,59].

Combining all 21 included studies on cefixime susceptibility, a total of 118 isolates with a MIC of cefixime >0.25 mg/L were identified in six countries, all belonging to developed nations. Among them, the United States had the highest number of non-susceptible NG isolates. Furthermore, the first non-susceptible isolate was also identified there, which might be attributable to the country's advanced and comprehensive monitoring system.

Cefpodoxime has been used as an alternative to cefixime, and the susceptibility rates of NG isolates to the two drugs were previously thought to be similar. However, based on our statistical analysis of the data, the susceptibility rate in NG isolates to cefixime was higher than that to cefpodoxime. The cefpodoxime susceptibility rate reported in Japan was lower than that in other countries where all tested isolates were susceptible to it. Treatment failure with cefpodoxime has not been reported yet, which might be due to the fact that it was less widely used to treat NG infection than cefixime.

To our knowledge, this is the first systematic review of globally published papers on cefixime and cefpodoxime susceptibility rates in NG isolates. Because the included studies varied by quality, the following limitations in this review should be acknowledged. First,

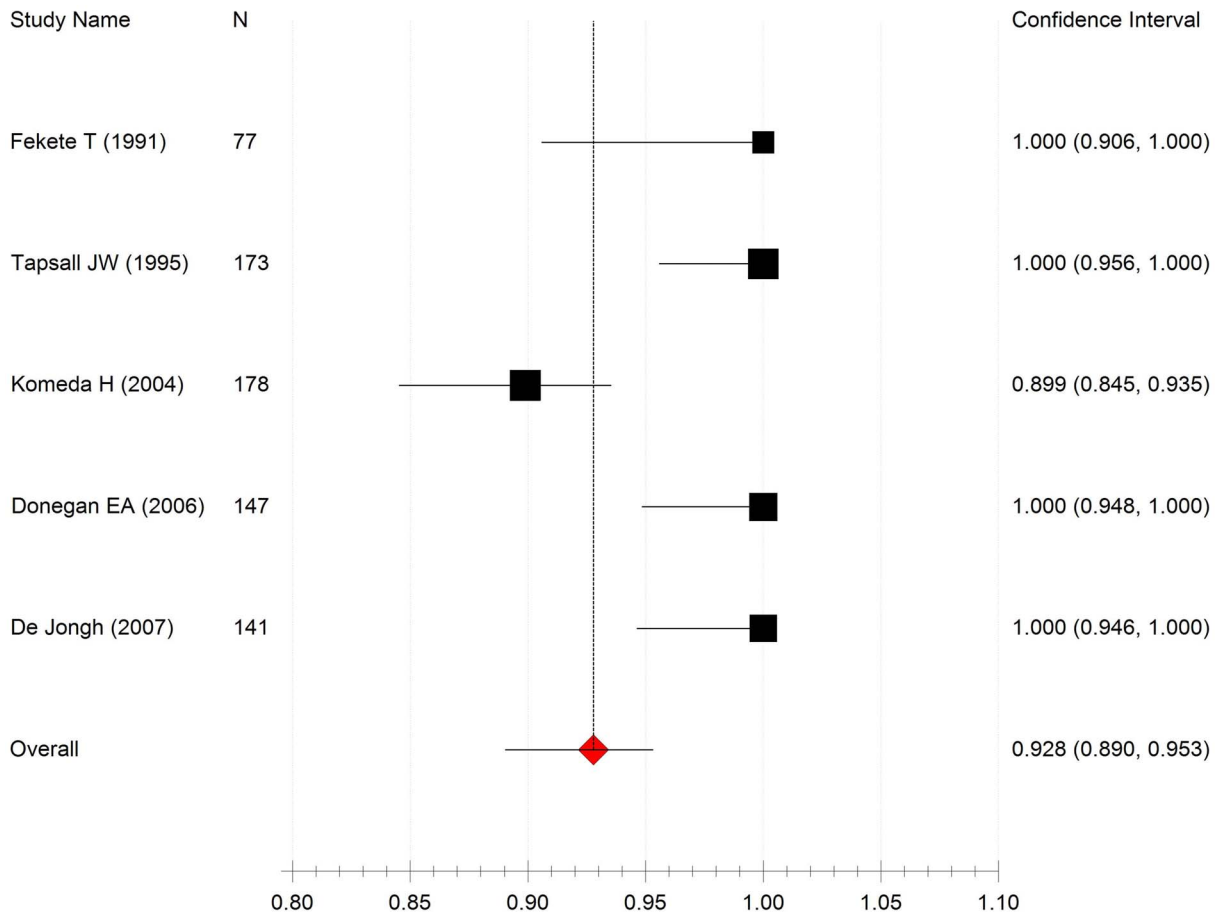


Figure 3. Forest plot of cefpodoxime susceptibility rates in NG isolates from five included studies. Heterogeneity ($I^2 = 44.6\%$, $P < 0.001$). doi:10.1371/journal.pone.0087849.g003

some studies had a small sample size of tested NG isolates, resulting in limited statistical power. Second, moderate heterogeneity still existed, which might be attributable to the differences in isolate identification method, media and control strains for MICs testing, and laboratory conditions among included studies. Third, some included studies did not describe the study population and/or isolate collection period. Fourth, there was a selection bias, leading to exclusion of relevant studies from some countries, because MICs of antibiotics were not determined using the standard agar dilution method in those studies. Finally, this review only evaluated published studies, without analyzing original data.

Although in general NG isolates are still highly susceptible to cefixime and cefpodoxime, reduced susceptibility rates were observed in some countries, especially in Japan, and in some populations such as men, which calls for a better control of gonococcal disease and an enhanced global surveillance of drug resistance [3,63]. Also, given that cefixime susceptibility rate has significantly decreased since 2003, leading to an increasing incidence of treatment failures with cefixime, and emergence of cefixime-resistant NG isolates, more attention should be paid to develop a wider range of antibiotic options and to stress the importance of cautious use of antibiotics. Future studies on the susceptibility rates of NG isolates to cefixime and cefpodoxime should at least take into account the following aspects. First, they need to describe the study population and the demographic characteristics and clinical history of patients, specify the method

of strain identification, and use the control strains recommended by the WHO in determining MICs. Second, at least some studies should be conducted in developing countries and those countries, in which use of these antibiotics is not recommended. Third, standard antimicrobial susceptibility testing method should be adopted. In addition, new antibiotic agents should be developed to treat NG infection and their efficacy should be monitored.

Supporting Information

Table S1 PubMed Search items.
(DOC)

Table S2 PRISMA 2009 checklist of the paper.
(DOCX)

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Author Contributions

Conceived and designed the experiments: YPY R-XY. Performed the experiments: R-XY G-QW QL. Analyzed the data: R-XY G-QW. Contributed reagents/materials/analysis tools: S-CC B-JZ X-QD. Wrote the paper: R-XY YPY. Edit the paper: YPY S-CC B-JZ X-QD YH G-YZ X-SC.

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