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Asymptomatic infections with *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* among women in lowand middle-income countries: A systematic review and meta-analysis

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# Abstract

Syndromic management of sexually transmitted infections (STIs) is common in settings with limited access to diagnostic testing. However, this approach does not capture asymptomatic STIs. Untreated asymptomatic infections may result in serious complications and sequelae in women. We aimed to estimate the proportion and the prevalence of asymptomatic Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG), and Trichomonas vaginalis (TV) infections among women in low- and middle-income countries. We searched Medline, Scopus, and Web of Science for articles published between 2000 and 2022. We used random effect models to compute the proportion and prevalence estimates and performed subgroup analysis. We evaluated the quality of each article using the Appraisal tool for Cross-Sectional Studies and performed sensitivity analyses. This study was registered with PROSPERO, CRD42022286673. Forty-eight eligible studies were included. The proportion of asymptomatic CT, NG, and TV infections were: 60.7% [95% Confidence Interval (CI): 50.4; 70.5], 53.3% [37.1; 69.1], and 56.9% [44.6; 68.9], respectively. The proportion of women with asymptomatic infections was the highest in Africa for the three pathogens. The pooled prevalence of asymptomatic CT, NG, and TV infection was 4.70 per 100 women [95%CI: 3.39; 6.20], 3.11 [1.34; 5.54], and 5.98 [3.46; 9.12], respectively. More than half of the women infected by CT, NG, or TV were asymptomatic. To avoid undiagnosed and untreated asymptomatic infections leading to complications, alternative approaches to syndromic management urgently need to be considered.

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# Introduction

More than one million sexually transmitted infections (STI) are acquired everyday worldwide [1]. Most of the infections by *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), and *Trichomonas vaginalis* (TV) occur in low- and middle-income countries (LMICs) [2].

The gold standard to detect these STIs are the Nucleic Acid Amplification Tests (NAATs); other methods include microscopy and bacterial culture [3]. Whilst high-income countries have developed screening programs [4] and use molecular methods, in most LMICs access to biological methods is hindered by the cost of diagnostics, lack of laboratory facilities and infrastructure, and trained personnel [5].

Therefore, STI detection and treatment in LMICs often rely on the syndromic management [6, 7]. However, asymptomatic STI cases are not captured by this approach, leaving a fraction of those infected undiagnosed and untreated.

In women, untreated infections caused by CT and NG can result in serious complications such as pelvic inflammatory disease (PID), infertility, and ectopic pregnancy [8]. Untreated trichomoniasis in pregnant women is associated with preterm birth or low birth weight [9]. These STIs are also associated with a higher risk of acquiring and transmitting other STIs, including HIV [10]. Lastly, untreated infections sustain the transmission.

To date, no study has provided pooled estimates of the burden of asymptomatic infections of the three most common curable STIs.

In this perspective, we conducted a systematic review and a meta-analysis to estimate: (i) the proportion of asymptomatic women among those infected by CT, NG, and TV and, (ii) the prevalence of asymptomatic CT, NG, and TV infections in the female population in LMICs.

## Methods

#### Search strategy

We searched MEDLINE, Web of Science, and Scopus databases. Search terms combined pathogen and disease terms, terms related to the absence of symptoms and countries ever classified as LMICs by the World Bank between 2000 and 2022 [11] (full search terms in S1 Text). We also screened references for eligible articles. When the estimates were collected but not presented, we contacted the authors up to three times.

#### Definitions

We defined "proportion of asymptomatic infection" as the number of women who tested positive for a pathogen and were asymptomatic divided by the number of women positive for that pathogen. We defined "prevalence of asymptomatic infection" as the number of women who tested positive for a pathogen and were asymptomatic divided by the number of women tested for that pathogen (S2 Text).

We defined symptoms as manifestations of a disease that were reported by the participant, while signs were considered features of a disease observed by a healthcare provider.

## Selection criteria

We selected studies published between 1 January 2000 and 31 December 2022, in English and French. We included studies which tested for STIs using genital or urine specimens. We kept studies that used NAATs for the diagnosis of CT, NG, and TV [3]. For TV, we also included articles that used InPouch or performed wet mount microscopy immediately after collection,

as these techniques showed fair sensitivity and specificity [12] and remain common detection methods in LMICs [13].

We selected studies where the investigator actively asked about at least one symptom, or where participants self-reported symptoms. We excluded articles in which authors assumed the absence of symptoms in the entire study population without collecting such information. Finally, we excluded articles when "asymptomatic" was defined as the absence of clinical signs as reported by the healthcare provider rather than by the women as we intended a participantcentred approach.

BTH, TC, RR, and CF conducted initial screening of titles and abstracts in pairs and inclusion conflicts were resolved through consensus. CF performed data extraction, and BTH, TC, and RR ensured exactness and validity. When multiple publications on the same study population and outcomes were found, we prioritized the most comprehensive and recent data. Extracted data included the number of asymptomatic positive women, total women tested, and women positive for a specific STI. Other variables we extracted were: first author, publication year, study year, country, recruitment site, number and type of reported symptoms, definition of asymptomatic women, rural/urban setting, specific populations (female sex works (FSWs), adolescents, women with HIV, adolescents, infertile women), age range, specimen type, other STI pathogens tested for, and detection techniques.

#### Data analysis

We described regions, study designs, settings, recruitment sites, specific populations, number of symptoms, sampling methods, and laboratory procedures of the selected studies.

Proportion and prevalence of asymptomatic CT, NG, and TV infections were estimated first for all studies and excluding studies on FSWs, women with HIV, and women attending an STI clinic as they are not representative of the general population and have a higher risk of having an STI. We referred to these groups as "populations with an increased risk of STIs". Separate estimations were conducted for FSWs, women with HIV as well as other key populations such as pregnant women, adolescents, and infertile women.

Random-effect models were applied for each of the above analyses using the DerSimonian and Laird variance estimator. As some figures were near 0 or 1, the Freeman-Tukey double arcsine transformation was applied. Statistical heterogeneity was evaluated using the  $\chi^2$  test with Cochran's Q and I<sup>2</sup>. Analyses and forest plots were conducted using *meta* and *metafor* packages in R software (version 4.1.1). Proportions and prevalence maps were generated using qGIS (version 3.22).

Subgroup analyses were performed by region, country income level, rural/urban setting, study period, and the number of symptoms assessed in the study. The role of these study variables in the heterogeneity of the estimates were explored in meta-regressions.

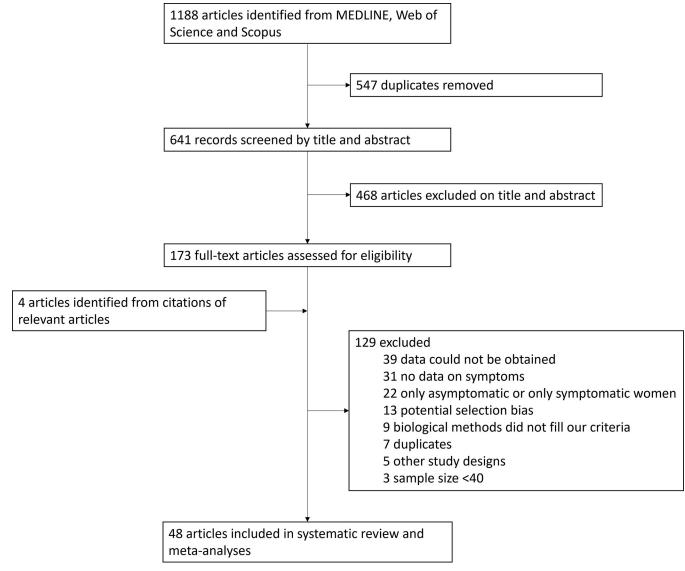
The risk of bias was assessed using the appraisal tool for cross-sectional studies (AXIS) using >70% of validated items as a cut-off to qualify studies with a low risk of bias [14]. We conducted a sensitivity analysis to assess the impact of excluding studies with a high risk of bias on our overall estimates.

Publication bias was evaluated by Funnel plots and the Egger test.

This article was written following the PRISMA checklist (S1 Table).

#### Results

We identified 1188 articles, among which 547 were duplicates. We eliminated 468 articles based on title and abstract and screened 173 full texts and their citations. We found 4 additional relevant citations among selected articles. In total, 177 articles were eligible. Of those, 42



#### Fig 1. Study selection.

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had available and extractable data and 45 reported having data according to our criteria but did not present the numbers. We were able to contact 40 of those 45 authors and retrieved data from six articles. In total, we used data from 48 studies corresponding to 99 data points for both the proportion and the prevalence: 41 for CT, 27 for NG, and 31 for TV (Fig 1, S2 Table, S3 Text). Twenty-one countries were represented in our study: eight in Africa, seven in Asia, five in Latin America, and one in Oceania. Most studies were cross-sectional (44/48, 92%) and few were cohort (2/48, 4%) or randomized controlled trials (2/48, 4%). Almost three-quarters of the studies (34/48, 71%) took place in urban settings, 21% (10/48) in rural settings, and 8% (4/48) in mixed settings. Hospitals and antenatal care were the most frequent recruitment sites (14/48, 29% and 11/48, 23%, respectively), followed by primary or secondary health care centres (9/48, 19%), locations where people with a high risk of STI can be found such as FSW venues, HIV centres or STI clinics (8/48, 17%). Six studies performed random sampling within the community (6/48, 13%). Some studies focused on specific populations: 15/48 (31%) were on pregnant women, 5/48 (10%) on FSWs, 4/48 (8%) on adolescents, 4/48 (8%) on women with HIV, and 4/48 (8%) on infertile women exclusively. Studies had enrolled between 48 and 4812 participants, and their age ranged from 10 to 90 years old although this information was unavailable for 14 studies.

The number of recorded symptoms ranged from one to 14, with more than half of the studies (23/48, 48%) exploring 1–4 symptoms.

Genital specimens (41/48, 85%) were the most common specimens, and few studies used urine (7/48, 15%). All techniques used for the laboratory diagnosis of CT (n = 41) and NG (n = 27) were NAATs, as per research criterium. For TV, NAATs were used in 25/31 studies, wet mount microscopy in 4/31, and InPouch in 2/31 studies.

The estimates summarised below are presented in Table 1, Figs 2 and 3, and S3–S5 Tables. The proportion of asymptomatic CT, NG, and TV infections, excluding populations with an increased risk of STIs, was 60.7% 95%CI [50.4; 70.5] (33 data points, 26 268 participants), 53.3% [37.1; 69.1] (21 data points, 16 950 participants), and 56.9% [44.6; 68.9] (23 data points, 10 824 participants), respectively.

The proportion of asymptomatic CT, NG, and TV infections (excluding populations with an increased risk of STIs) was significantly different across regions (p = 0.048, p = 0.019, and p = 0.039, respectively for each pathogen). Africa presented the highest proportion of asymptomatic infections (CT: 68.6% [56.4; 79.8], 14 data points, 12 368 participants; NG: 67.2% [51.0; 81.9], 13 data points, 7 681 participants; TV: 64.9% [52.2; 76.7], 12 data points, 6 152 participants). Latin America had the lowest proportion of asymptomatic women infected with CT (30.9% [11.2; 54.8], five data points, 2 850 participants) and with NG (14.0% [0.0; 67.5], two data points, 1 546 participants). The lowest proportion of asymptomatic TV infection was found in Asia (17.3% [0.0; 49.5], four data points, 2 606 participants).

When stratifying by country income level, the proportions of asymptomatic cases were the highest in middle-income countries (CT: 63.2% [50.2; 75.1], 11 data points, 14 887 participants; NG: 60.9% [41.1; 79.2], 14 data points, 10 793 participants; TV: 61.7% [45.4; 77.1], 17 data points, 6 688 participants), and the lowest in low-income countries (CT: 55.5% [37.3; 73.1], 11 data points, 11 381 participants; NG: 37.7% [18.4; 58.8], seven data points, 6 157 participants; TV: 45.4% [29.7; 61.6], six data points, 4 136 participants). The proportion of asymptomatic infected women was also the highest in rural settings (CT: 71.6% [55.6; 85.3], ten data points, 9 150 participants; NG: 70.4% [46.3; 90.3], 9 data points, 4 464 participants; TV: 75.0% [49.8; 94.0], six data points, 2 619 participants), and the lowest in urban settings (CT: 55.6% [43.8; 67.1], 20 data points, 15 276 participants; NG: 44.4% [26.5; 62.9], 11 data points, 12 124 participants; TV: 58.9% [46.5; 70.8], 15 data points, 7 544 participants).

Analyses on specific populations showed that, in women with HIV, the proportion of asymptomatic CT, NG, and TV infections exceeded 50% (CT: 64.7% [48.3; 79.7], three data points, 739 participants; NG: 61.0% [42.7; 78.0], three data points, 739 participants; TV: 70.5% [60.7; 79.6], four data points, 965 participants). In FSWs, those proportions were below 50% (CT: 45.5% [24.8; 67.0], five data points, 1 890 participants; NG: 38.1% [3.1; 82.9], three data points, 1 051 participants; TV: 26.7% [19.6; 34.5], two data points, 546 participants).

The prevalence of asymptomatic women infected with CT, NG, or TV was 4.70 per 100 women [3.39; 6.20] (33 data points, 26 268 participants), 3.11 [1.34; 5.54] (21 data points, 16 950 participants) and 5.98 [3.46; 9.12] (23 data points, 10 824 participants), respectively, excluding populations with an increased risk of STI infection.

The prevalence of asymptomatic NG and TV infections differed significantly across regions (p<0.001). The highest prevalence was found in Africa and Oceania (NG: 5.67 [2.15; 10.66] and 3.12 [0.00; 12.25], TV: 9.06 [5.71; 13.07] and 12.77 [0.06; 40.12], respectively) and the lowest in Asia and Latin America (NG: 0.13 [0.03; 0.28] and 0.12 [0.00; 1.16], TV: 0.08 [0.00; 0.31]

	Proportion	n of asymptomati	c infections	Prevalence	Prevalence of asymptomatic infections			
	(per 100	(per 100 infected women) [95%CI]			(per 100 tested women) [95%CI]			
	СТ	NG	TV	СТ	NG	TV		
Overall								
Excluding populations with an increased risk of STI*	60.7 [50.4; 70.5]	53.3 [37.1; 69.1]	56.9 [44.6; 68.9]	4.70 [3.39; 6.20]	3.11 [1.34; 5.54]	5.98 [3.46; 9.12]		
Including populations with an increased risk of STI	58.8 [50.4; 67.0]	52.2 [38.5; 65.6]	53.6 [43.0; 64.1]	6.05 [4.26; 8.12]	3.70 [1.79; 6.23]	5.84 [3.75; 8.34]		
Continent*								
Africa	68.6 [56.4; 79.8]	67.2 [51.0; 81.9]	64.9 [52.2; 76.7]	4.99 [2.70; 7.90]	5.67 [2.15; 10.66]	9.06 [5.71; 13.07]		
Asia	66.2 [47.2; 83.0]	27.7 [9.0; 50.9]	17.3 [0.0; 49.5]	5.55 [3.40; 8.19]	0.13 [0.03; 0.28]	0.08 [0.00; 0.31]		
Latin America	30.9 [11.2; 54.8]	14.0 [0.0; 67.5]	50.1 [16.4; 83.8]	1.89 [0.56; 3.91]	0.12 [0.00; 1.16]	4.54 [0.52; 11.9]		
Oceania	47.4 [2.7; 95.0]	32.7 [0.0; 88.3]	43.3 [4.8; 87.5]	7.22 [0.00; 24.73]	3.12 [0.00; 12.25]	12.77 [0.06; 40.12]		
Country income level*								
Low-Income	55.5 [37.3; 73.1]	37.7 [18.4; 58.8]	45.4 [29.7; 61.6]	3.55 [1.87; 5.70]	0.57 [0.17; 1.17]	3.12 [0.73; 7.02]		
Middle-Income	63.2 [50.5; 75.1]	60.9 [41.1; 79.2]	61.7 [45.4; 77.1]	5.34 [3.59; 7.39]	5.21 [1.77; 10.22]	7.28 [3.72; 11.88]		
Setting*								
Rural	71.6 [55.6; 85.3]	70.4 [46.3; 90.3]	75.0 [49.8; 94.0]	5.36 [3.11; 8.15]	6.80 [1.39; 15.60]	10.27 [2.41; 22.46]		
Urban	55.6 [43.8; 67.1]	44.4 [26.5; 62.9]	58.9 [46.5; 70.8]	4.83 [2.90; 7.19]	1.33 [0.29; 3.02]	4.81 [2.25; 8.21]		
Study year*								
1998-2011	61.8 [48.1; 74.7]	55.9 [32.9; 77.8]	57.3 [41.0; 73.0]	4.41 [2.37; 6.99]	3.72 [0.98; 7.99]	5.94 [2.86; 10.00]		
2011-2022	57.7 [42.1; 72.7]	48.9 [26.9; 71.1]	61.1 [41.3; 79.5]	4.09 [2.88; 5.49]	2.42 [0.47; 5.63]	6.99 [2.09; 14.30]		
Number of symptoms assessed*								
Between 1 and 4	57.4 [41.6; 72.4]	40.6 [13.8; 70.4]	55.1 [37.7; 71.9]	6.53 [3.46; 10.45]	4.39 [0.46; 11.76]	5.68 [2.97; 9.17]		
Five and more	69.0 [51.7; 84.2]	71.8 [56.6; 85.2]	63.6 [43.3; 81.9]	4.29 [2.48; 6.53]	3.50 [1.27; 6.68]	7.66 [2.94; 14.24]		
Key population†								
Pregnant women	55.3 [40.6; 69.6]	45.7 [27.9; 63.9]	58.8 [43.9; 73.0]	7.50 [4.31; 11.44]	2.60 [1.27; 4.32]	7.96 [4.73; 11.91]		
Female sex workers	45.5 [24.8; 67.0]	38.1 [3.1; 82.9]	26.7 [19.6; 34.5]	13.63 [2.76; 30.72]	9.49 [0.04; 30.73]	7.02 [4.16; 10.52]		
Adolescents	57.4 [17.9; 92.2]	35.9 [15.0; 59.2]	46.4 [27.6; 65.7]	1.89 [1.55; 2.27]	1.12 [0.01; 3.59]	2.05 [0.33; 4.98]		
Women with HIV	64.7 [48.3; 79.7]	61.0 [42.7; 78.0]	70.5 [60.7; 79.6]	10.11 [0.13; 31.39]	3.09 [0.68; 6.96]	6.42 [1.89; 13.23]		
Infertile	74.7 [59.9; 87.2]		100 [5.5; 89.2]	11.76 [4.33; 22.07]	0.00 [0.07; 3.40]	0.73 [0.04; 4.60]		

#### Table 1. Proportion and prevalence of asymptomatic CT, NG, and TV infections in women in LMICs.

\* These analyses excluded populations with an increased risk of STI (FSW, women with HIV, and women attending an STI clinic)

† These analyses were conducted exclusively on these populations and did not consist of a sub-group analysis. "Pregnant women" and "Women with HIV" are not mutually exclusive

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	Study	Events	Total	Events per 100 observations	Events	95%-CI	Weight
A	Claeys, 2002 Cabeza, 2015 Mahafzah, 2008 Wangnapi, 2015 Silveira, 2020 Hokororo, 2015 Chang, 2020 Jenab, 2010 Warr, 2019 Ghebremichael, 2014 Li, 2021 Mbizvo, 2001 Karim, 2021 Lan, 2008 Rocha, 2014 Moodley, 2015 Li, 2021 Hoffman, 2019 Mania–Pramanik, 2012 Davey, 2019 Kerubo, 2016 Conde–Ferráez, 2017 Peters, 2014 Badman, 2016 Mania–Pramanik, 2012 Obasi, 2001 Li, 2021 Gokral, 2005 Kalsom, 2020 Hazel, 2014 Frohlich, 2007 Chen, 2020	$\begin{array}{c} 3 \\ 8 \\ 1 \\ 1 \\ 8 \\ 8 \\ 6 \\ 1 \\ 1 \\ 1 \\ 1 \\ 8 \\ 6 \\ 6 \\ 2 \\ 8 \\ 1 \\ 1 \\ 1 \\ 8 \\ 1 \\ 1 \\ 1 \\ 8 \\ 1 \\ 1$	40 60 7 39 44 46 404 404 404 47 65 25 53 55 52 47 28 33 55 24 13 315 97 7 28 34 40 34 415 97 25 24 413 15 97 25 24 413 15 25 9 97 25 24 413 15 52 24 40 40 40 40 40 40 40 40 40 40 40 40 40		13.33 14.29 20.51 32.91 34.16 35.29 51.43 53.85 53.85 55.81 55.81 55.81 55.81 55.81 55.81 55.81 55.81 55.81 55.81 66.23 77.33 77.16 63.83 67.86 68.23 77.33 77.16 88.29 76.00 79.17 76.00 79.10 76.00 79.10 76.00 79.10 76.00 79.10 76.00 79.10 76.00 79.10 76.00 79.10 76.00 79.10 70.00 79.10 70.000	$\begin{array}{c} [29.58; 39.04] \\ [15.26; 61.38] \\ [31.06; 55.92] \\ [2.67; 97.33] \\ [2.67; 97.33] \\ [24.28; 68.28] \\ [27.42; 77.72] \\ [26.12; 79.60] \\ [34.28; 68.28] \\ [27.42; 77.72] \\ [26.12; 79.60] \\ [34.28; 77.61] \\ [32.89; 82.54] \\ [48.37; 76.12] \\ [38.88; 89.64] \\ [48.39; 76.91] \\ [47.57; 83.42] \\ [48.48; 76.94] \\ [47.57; 83.42] \\ [48.48; 76.94] \\ [47.57; 83.42] \\ [48.48; 76.94] \\ [47.57; 83.42] \\ [48.48; 76.94] \\ [47.57; 83.42] \\ [48.48; 76.94] \\ [47.57; 83.42] \\ [48.48; 76.94] \\ [47.57; 83.42] \\ [48.48; 76.94] \\ [47.57; 83.42] \\ [48.48; 76.94] \\ [47.57; 83.42] \\ [48.48; 91.06] \\ [59.46; 85.66] \\ [70.52; 93.16] \\ [59.48; 89.765] \\ [76.88; 99.763] \\ [79.95; 99.54] \\ [90.00; 99.79] \end{array}$	3.2% 3.2% 3.2% 3.2% 3.2% 3.5% 2.9% 3.3% 1.4% 3.2% 2.9% 3.2% 3.2% 2.9% 3.2% 3.2% 3.2% 3.3% 3.5% 2.9% 3.3% 3.1% 3.1% 3.1% 3.1% 3.1% 3.1% 3.1% 3.1% 3.2% 3.2% 3.2% 3.2% 3.1% 3.1% 3.1% 3.1% 3.2% 3.0%
В	Random effects model Heterogeneity: / <sup>2</sup> = 93%, T Claeys, 2002 Wangnapi, 2015 Chang, 2020 Warr, 2019		<b>1718</b> 0, <i>p</i> < 0 5 32 43 29		0.00 9.38 16.28	[ <b>50.48</b> ; <b>70.48</b> ] [ 1.87; 53.71] [ 2.45; 26.17] [ 7.33; 31.30] [11.02; 43.93]	4.1% 5.6% 5.8% 5.6%
	Mahafzah, 2008 Mbizvo, 2001 Hokororo, 2015 Rocha, 2014 Moodley, 2015 Lan, 2008 Kerubo, 2016 Davey, 2019 Badman, 2016 Peters, 2014 Hoffman, 2019 Ghebremichael, 2014 Karim, 2021 Frohlich, 2007 Hazel, 2014 Frohlich, 2007	4 2 9 2 4 9 4 2 2 9 41 27 177 83 2 1388 15	14 7 5 93 7 3 14 60 39 24 113 2 150 15		28.57 28.57 33.33 40.00 52.69 57.14 66.67 64.29 68.33 69.23 70.83 73.45 100.00 92.00 100.00	[9.58; 58.00] [5.11; 69.74] [7.24; 53.98] [7.26; 82.96] [20.24; 88.19] [12.53; 98.23] [35.63; 86.02] [54.91; 79.40] [52.27; 82.45] [48.75; 86.56] [64.17; 81.11] [76.14; 95.61] [74.65; 99.39]	5.1% 4.5% 5.6% 4.1% 5.9% 4.5% 3.4% 3.4% 5.1% 5.7% 5.5% 6.0% 2.9% 6.0% 5.2%
	Random effects model Heterogeneity: / <sup>2</sup> = 92%, т		<b>685</b> ), p < 0	.01 20 40 60 80	53.26	[37.09; 69.14]	100.0%
c	Mucci, 2016 Mahafzah, 2008 Shehabi, 2009 Bruni, 2019 Wangnapi, 2015 Adeoye, 2007 Tann, 2006 Lan, 2008 Rocha, 2014 Kerubo, 2016 Moodley, 2015 Mabaso, 2020 Hoffman, 2019 Ghebremichael, 2014 de Waaij, 2017 Mbizvo, 2001 Badman, 2016 Miranda, 2014 Davey, 2019 Kalsom, 2020 Lopez–Monteon, 2013 Frohlich, 2007 Random effects model	0 4 15 4 13 3 21 6 118 28 50 94 75 40 32 16 12 1 45 10 54	3 9 1 21 73 18 43 10 46 12 223 47 81 152 113 60 47 23 160 1 1 48 10 54 <b>1111</b>		$\begin{array}{c} 11.11\\ 0.00\\ 19.05\\ 20.55\\ 22.22\\ 30.23\\ 30.00\\ 45.65\\ 50.00\\ 52.91\\ 59.57\\ 61.73\\ 61.84\\ 66.37\\ 68.09\\ 69.57\\ 75.00\\ 100.00\\ 93.75\\ 100.00\\ 100.00\\ \end{array}$	[3.18; 69.00] [0.58; 49.33] [10.78; 94.54] [6.29; 42.58] [12.32; 31.93] [17.37; 48.08] [17.67; 46.30] [8.09; 64.63] [31.18; 60.84] [22.29; 77.71] [46.15; 59.56] [50.22; 72.11] [53.58; 69.49] [53.26; 74.82] [53.27; 77.98] [52.75; 80.48] [46.99; 85.94] [54.69; 922] [81.79; 98.37] [55.55; 99.08] [91.73; 99.83] [44.62; 68.91]	2.4% 3.7% 4.5% 5.2% 4.4% 5.0% 3.9% 5.0% 4.0% 5.4% 5.3% 5.3% 5.3% 5.3% 5.1% 5.0% 4.6% 4.6% 4.6% 4.3% 1.4% 5.0% 3.9% 5.1%
	Random effects model Heterogeneity: $l^2 = 91\%$ , T			.01 20 40 60 80	56.94	[44.62; 68.91]	100.0%

Fig 2. Forest plots of the proportion of asymptomatic CT (A), NG (B) and TV (C), in women, in LMICs.

https://doi.org/10.1371/journal.pgph.0003226.g002

	Study	Events	Total	Events per 100 observations	Events	95%-CI	Weight
A	Ghebremichael, 2014 Mahafzah, 2008 Claeys, 2002 Karim, 2021 Gabeza, 2015 Silveira, 2020 Keruba, 2016 Obasi, 2001 Mbizvo, 2001 Warr, 2019 Wangnapi, 2015 Lan, 2008 Hokororo, 2015 Chang, 2020 Li, 2021 Li, 2021 Rocha, 2014 Chen, 2020 Li, 2021 Rocha, 2014 Chen, 2020 Li, 2021 Frohlich, 2007 Frohlich, 2007 Kalsom, 2020 Mania–Pramanik, 2012 Hazel, 2014 Mania–Pramanik, 2012 Peters, 2014 Hoffman, 2019 Davey, 2019 Badman, 2016 Gokral, 2005		1440 1275 1185 807 4468 4686 4686 4686 4686 4686 481 221 362 4686 80 226 4812 4812 4812 4812 4812 4812 4812 4812		8.33 9.49 10.14 10.92 11.11 11.36 11.88 13.15 14.07 15.20 29.00	[5.62; 13.53] [2.70; 20.87] [5.35; 15.99] [8.67; 11.84] [6.87; 16.76] [7.32; 16.40] [7.92; 15.97] [9.44; 14.84] [9.35; 18.11]	3.3% 3.3% 3.2% 3.2% 3.1% 3.3% 3.1% 3.3% 3.1% 3.1% 3.2% 3.1% 3.2% 3.1% 3.2% 3.1% 3.2% 3.1% 3.2% 3.0% 3.2% 3.0% 2.4% 2.9% 2.4% 2.9% 3.3% 3.2% 3.0% 2.6% 2.6%
	Heterogeneity: / <sup>2</sup> = 96%, т	<sup>2</sup> = 0.0083	, <i>p</i> < 0.01	10 20 30			
В	Claeys, 2002 Chang, 2020 Kalsom, 2020 Mahafzah, 2008 Lan, 2008 Kerubo, 2016 Warr, 2019 Mbizvo, 2001 Rocha, 2014 Wangnapi, 2015 Ghebremichael, 2014 Davey, 2019 Hokororo, 2015 Moodley, 2015 Frohlich, 2007 Frohlich, 2007 Frohlich, 2007 Peters, 2014 Badman, 2016 Karim, 2021 Hoffman, 2019 Hazel, 2014 <b>Random effects model</b> Heterogeneity: <i>I</i> <sup>2</sup> = 98%, 1		1185 4812 137 1275 1012 507 1221 389 361 362 1440 135 403 1458 48 - 226 589 1255 807 251 207 <b>1</b> 275 <b>1</b> 400 <b>1</b> 35 <b>4</b> <b>1</b> 400 <b>1</b> 35 <b>1</b> 226 <b>5</b> 89 <b>1</b> 251 207 <b>2</b> 51 207 <b>1</b> 207 <b>1</b> 207 <b>1</b> 207 <b>1</b> 207 <b>1</b> 207 <b>1</b> 35 <b>1</b> 207 <b>1</b> 400 <b>1</b> 35 <b>1</b> 458 <b>1</b> 458 <b>1</b> 458 <b>1</b> 25 <b>1</b> 207 <b>1</b> 207 <b>1</b> 207 <b>1</b> 207 <b>1</b> 35 <b>1</b> 458 <b>1</b> 25 <b>1</b> 207 <b>1</b> 207 <b></b>		6.64 6.96 7.20 10.29 10.76 66.67 <b>3.11</b>	[ 0.06; 0.31] [ 0.07; 3.40] [ 0.10; 0.86] [ 0.13; 1.08] [ 0.07; 1.58] [ 0.05; 1.23] [ 0.09; 2.05] [ 0.10; 2.21] [ 0.71; 1.92] [ 0.72; 2.61] [ 0.72; 5.79] [ 1.09; 4.35] [ 2.52; 4.45] [ 0.72; 15.43] [ 3.89; 10.93]	4.9% 5.0% 4.5% 4.9% 4.9% 4.9% 4.8% 4.8% 4.8% 4.8% 4.5% 4.5% 4.5% 4.9% 3.9% 4.7% 4.9% 4.7% 4.7% 4.7%
c	Mahafzah, 2008 Mucci, 2016 Shehabi, 2009 Lan, 2008 Adeoye, 2007 Bruni, 2019 Kalsom, 2020 Kerubo, 2016 Wangnapi, 2015 Miranda, 2014 Tann, 2006 Rocha, 2014 Ghebremichael, 2014 Mabaso, 2020 Moodley, 2015 Mbizvo, 2001 Davey, 2019 de Waaij, 2017 Hoffman, 2019 Frohlich, 2007 Lopez-Monteon, 2013 Frohlich, 2007 Badman, 2016	$\begin{array}{c} 1 \\ 0 \\ 0 \\ 3 \\ 4 \\ 4 \\ 1 \\ 6 \\ 15 \\ 16 \\ 13 \\ 21 \\ 94 \\ 28 \\ 118 \\ 40 \\ 12 \\ 75 \\ 50 \\ 10 \\ 45 \\ 54 \\ 32 \end{array}$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	-	0.08 0.00 0.30 0.74 0.80 0.73 1.18 4.14 5.35 5.33 5.33 5.82 6.53 7.73 8.09 10.28 11.21 13.04 19.92 20.83 21.43 23.89 25.60	0.05; 2.58] (0.08; 0.94] (0.24; 2.01] (0.24; 2.01] (0.45; 2.18] (0.44; 4.60] (1.45; 2.68] (2.42; 6.89] (2.42; 6.89] (3.19; 8.72] (2.99; 9.15] (3.73; 8.89] (5.29; 11.11] (6.76; 9.64] (5.75; 13.84) (6.76; 9.64] (7.53; 13.84) (1.64; 16.14; 19.14] (10.46; 16.14] (10.46; 16.14] (10.46; 16.14] (10.46; 16.14] (10.42; 16.14] (10.44] (1	$\begin{array}{c} 4.5\%\\ 4.3\%\\ 4.3\%\\ 4.5\%\\ 4.5\%\\ 4.5\%\\ 4.2\%\\ 4.2\%\\ 4.4\%\\ 4.3\%\\ 4.4\%\\ 4.3\%\\ 4.4\%\\ 4.4\%\\ 4.4\%\\ 4.4\%\\ 4.1\%\\ 4.4\%\\ 4.1\%\\ 4.1\%\\ 4.4\%\\ 4.6\%\\ 4.6\%\\ 4.6\%\\ 4.3\%\\ 4.3\%\\ 4.3\%\\ 4.2\%\end{array}$
	Random effects model Heterogeneity: $l^2 = 97\%$ , T		<b>10824</b> , p < 0.01	5 10 15 20 25 30 33		[ 3.46; 9.12]	100.0%
	• F • 1 ·	6.1	,	<u> </u>		1) 110 (7)	1 1 1 1 1 1 1 1

Fig 3. Forest plots of the prevalence of asymptomatic CT (A), NG (B) and TV (C), in women, in LMICs.

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and 4.54 [0.52; 11.9], respectively). A similar pattern was observed for CT, but there was weak evidence of this difference (p = 0.068).

For NG only, the prevalence of asymptomatic infection was significantly higher in middleincome countries versus low-income (5.21 [1.77; 10.22] vs 0.57 [0.17; 1.17], p = 0.002) and was nearly significantly different between rural and urban settings (6.80 [1.39; 15.60] vs 1.33 [0.29; 3.02], p = 0.059).

Relative to the other key populations, the prevalence of asymptomatic CT, NG, and TV was low among adolescents (CT: 1.89 [1.55; 2.27]; NG: 1.12 [0.01; 3.59]; TV: 2.05 [0.33; 4.98]) and high among FSWs (CT: 13.6 [2.76; 30.72]; NG: 9.49 [0.04; 30.73]; TV:7.02 [4.16; 10.52]).

Proportion and prevalence by country are presented in Fig 4 and S6 Table.

After excluding studies with a high risk of bias, our sensitivity analyses showed no significant change in our findings (S7–S9 Tables). Results of the meta-regression showed that the continent and the country income level explained a substantial part of the variation in our estimates (S10 Table). Results from the Funnel plots and Egger's tests showed no evidence of publication bias (S1–S3 Fig).

## Discussion

Our study reveals a significant public health challenge: more than half of the women infected with CT, NG, and TV were asymptomatic in LMICs. The prevalence of asymptomatic infections ranged from 3 to 6%. When cumulating the prevalence of each of pathogen, accounting for the rarity of co-infections, [15, 16] the prevalence could reach up to 13%. These high proportions and prevalence of asymptomatic infections are particularly worrisome since those women remain untreated and thus may develop serious complications. Additionally, they constitute an unseen reservoir that continues to fuel the STI epidemic.

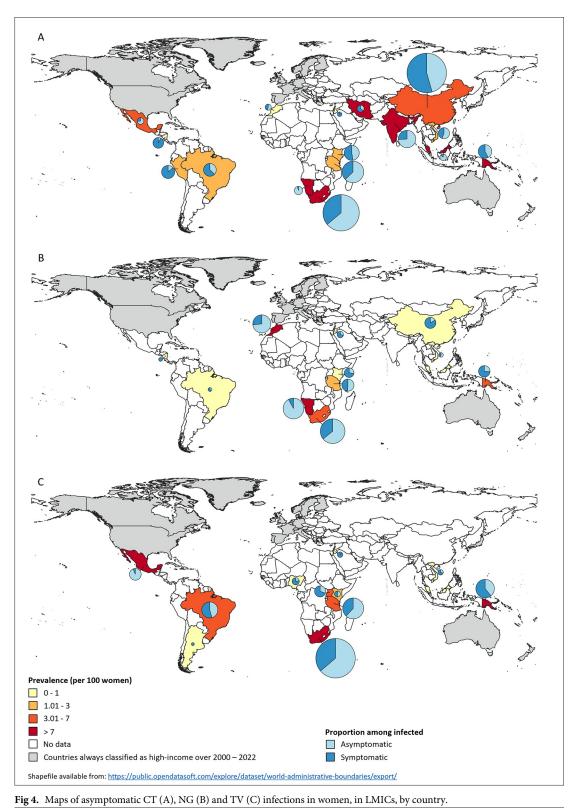
Several hypotheses can be proposed to explain these high estimates. First, women may have difficulties in distinguishing physiological from abnormal vaginal discharge. For instance, in Tanzania, a study found that more than two third of women with abnormal discharge did not report any symptoms [17]. In rural areas of Madagascar, anthropologists reported that genital symptoms are thought to be normal [18] and women may not report them, even after probing.

Alternatively, social norms may prevent women from declaring their symptoms. They may correctly identify genital symptoms but may be unwilling to communicate them to healthcare professionals due to the stigma attached to such symptoms or fear of being judged [19].

The notably high proportions of asymptomatic CT, NG, and TV infections in Africa are concerning. STIs are associated with an increased risk of transmitting and acquiring other STIs or HIV and Africa bears amongst the highest STI and HIV prevalence in the world [2, 20]. The wide use of syndromic approach in Africa means that asymptomatic women are often left undiagnosed and untreated, posing a risk of transmission to their partners and contributing to adverse health outcomes.

We observed a high proportion of asymptomatic STIs among women with HIV. While the limited number of studies limits definitive conclusions, similar findings have been reported among men with HIV who have sex with men [21]. In this study, detectable plasma HIV RNA, social factors, and sexual practices were associated with asymptomatic STIs. Further research could also explore the potential immunological mechanisms underlying this phenomenon.

Our study revealed an elevated prevalence of asymptomatic STIs among FSWs. This reflects their increased susceptibility to STIs explained by their frequent engagement in sexual activities with multiple partners. However, we observed a relatively lower proportion of asymptomatic women, which could be explained by FSWs' increased awareness and recognition of STI symptoms [22].



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We found a low prevalence of asymptomatic STIs among adolescents, possibly due to the lower STI prevalence in this group and the inclusion of sexually inactive participants in some studies. However, despite the lower prevalence, adolescents remain vulnerable to STI acquisition due to their sexual behavior and physiological susceptibility [23]. Implementing comprehensive sexual education programs during early adolescence could effectively maintain a low STI occurrence in this key population [24].

This study has several limitations. Firstly, the majority of the studies were conducted in healthcare facilities which may introduce bias, as women could attend these facilities because of genitourinary symptoms, potentially underrepresenting asymptomatic cases compared to the general population. Consequently, while our estimates are already substantial, the true proportion and prevalence could be even higher. Furthermore, our search yielded only six articles conducted in community settings, indicating a gap in community-based research. Such studies are pivotal for accurately assessing the proportion and prevalence of asymptomatic STIs in the general population. Another limitation pertains to the varying number of symptoms used to determine symptomatic status, ranging from one to fourteen. Studies examining more symptoms were more likely to identify symptomatic cases and fewer asymptomatic cases. However, our comparison of estimates from studies assessing one to four symptoms versus those assessing five or more symptoms did not show any significant differences. Establishing a uniform definition in future research could potentially reduce the heterogeneity among different studies.

Another limitation of our review is that 39 studies appeared to have collected the data we needed but we were unable to obtain these figures. However, we did not find any temporal or spatial pattern among them. In addition, due to our language restrictions, ten studies conducted in Latin America were excluded although they seemed to be relevant.

Nevertheless, our study has several strengths. To the best of our knowledge, this is the first meta-analysis providing comprehensive estimated on asymptomatic STIs in LMICs among women. Our strict inclusion and exclusion criteria, particularly regarding pathogen identification techniques minimized the risk of including false positive cases and ensured that the study's findings were based on high-quality and reliable data. We also provided estimates for specific populations of pregnant women, FSWs, adolescents, women with HIV, and infertile women. Further research is needed. Within this large reservoir of asymptomatic STIs, it is important to estimate what percentage of women will develop complications such as PID as well as what percentage will spontaneously clear the pathogen [25] It is also critical to identify characteristics associated with developing complications or sequelae in order to treat those women at an early stage.

We showed that the prevalence and proportion of asymptomatic STIs among women in LMICs represent a significant public health concern. An alternative to the syndromic management could be the development of an easy-to-use and affordable point-of-care test (POCT) that would rapidly and accurately detect STIs [26]. A POCT to screen women with suspected STIs among asymptomatic women would be more cost-effective than POCT testing for each pathogen on all of them. Currently, a POCT detecting inflammation caused by any STI is being tested [27]. In addition to providing confidential healthcare services and destigmatizing STIs as defined in the global health strategies on STIs by the WHO for 2022–2030, [28] such a device could be used by health care providers to screen asymptomatic women in order to prevent adverse consequences for reproductive and overall health.

## Data sharing

The study protocol is available on PROSPERO (CRD42022286673). The equations for searching the databases are given in <u>S1 Text</u>. Countries' classifications into income levels are publicly available from the World Bank [11]. Data extracted from the studies (deidentified data) and the data dictionary are publicly available with no restriction at <u>https://doi.org/10.57745/</u>C61VFC.

# Supporting information

**S1 Text. Search terms for citation selection.** (DOCX)

**S2 Text. Formulae of the calculation of proportion and prevalence of asymptomatic infections. Formula:** Calculation of prevalence and proportion of asymptomatic infections. (DOCX)

**S3 Text. References of included articles.** (DOCX)

**S1 Table. PRISMA checklist.** (DOCX)

**S2** Table. List and characteristics of included articles. (DOCX)

S3 Table. Proportion and prevalence of asymptomatic CT infections: Number of studies, number of participants, and I<sup>2</sup>. (DOCX)

S4 Table. Proportion and prevalence of asymptomatic NG infections: Number of studies, number of participants, and I<sup>2</sup>. (DOCX)

S5 Table. Proportion and prevalence of asymptomatic TV infections: Number of studies, number of participants, and I<sup>2</sup>. (DOCX)

S6 Table. Sensitivity analysis-proportion and prevalence estimates of asymptomatic CT infections excluding high risk of bias studies. (DOCX)

S7 Table. Sensitivity analysis-proportion and prevalence estimates of asymptomatic NG infections excluding high risk of bias studies. (DOCX)

**S8** Table. Sensitivity analysis-proportion and prevalence estimates of asymptomatic TV infections excluding high risk of bias studies. (DOCX)

S9 Table. Proportion and prevalence of asymptomatic CT, NG, and TV by country (data used for the map).

(DOCX)

**S10 Table.** Meta-regression estimates and 95% CI for the proportion and the prevalence of asymptomatic CT (A), NG (B), and TV (C). (DOCX)

**S1** Fig. Funnel plot and Egger's test for the proportion of asymptomatic CT. (DOCX)

**S2** Fig. Funnel plot and Egger's test for the proportion of asymptomatic NG. (DOCX)

**S3** Fig. Funnel plot and Egger's test for the proportion of asymptomatic TV. (DOCX)

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CF, BTH, TC, and RVR conceived the study and research question. CF did the literature search with an information specialist, Catherine Cecilio. CF, BTH, TC, and RVR selected on titles and abstracts the results from the search strategy. CF extracted the data and BTH, TC, and RVR checked extracted data. CF did the analysis and wrote the first draft. BTH, TC, RVR and EDA wrote, edited, and revised the manuscript. CF, BTH, TC, and RVR had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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## **Author Contributions**

- **Conceptualization:** Camille Fortas, Rindra Vatosoa Randremanana, Tania Crucitti, Bich-Tram Huynh.
- **Data curation:** Camille Fortas, Rindra Vatosoa Randremanana, Tania Crucitti, Bich-Tram Huynh.
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- Validation: Elisabeth Delarocque-Astagneau, Rindra Vatosoa Randremanana, Tania Crucitti, Bich-Tram Huynh.
- Visualization: Camille Fortas, Rindra Vatosoa Randremanana, Tania Crucitti, Bich-Tram Huynh.
- Writing original draft: Camille Fortas.
- Writing review & editing: Elisabeth Delarocque-Astagneau, Rindra Vatosoa Randremanana, Tania Crucitti, Bich-Tram Huynh.

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