Global burden of recurrent vulvovaginal candidiasis: a systematic review

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Recurrent vulvovaginal candidiasis is a debilitating, long-term condition that can severely affect the quality of life of affected women. No estimates of the global prevalence or lifetime incidence of this disease have been reported. For this systematic review, we searched PubMed, Embase, and Web of Science databases for population-based studies published between 1985 and 2016 that reported on the prevalence of recurrent vulvovaginal candidiasis, defined as four or more episodes of the infection every year. We identified 489 unique articles, of which eight were included, consisting of 17 365 patients from 11 countries. We generated estimates of annual global prevalence, estimated lifetime incidence and economic loss due to recurrent vulvovaginal candidiasis, and predicted the number of women at risk to 2030. Worldwide, recurrent vulvovaginal candidiasis affects about 138 million women annually (range 103–172 million), with a global annual prevalence of 3871 per 100 000 women; 372 million women are affected by recurrent vulvovaginal candidiasis over their lifetime. The 25–34 year age group has the highest prevalence (9%). By 2030, the population of women with recurrent vulvovaginal candidiasis each year is estimated to increase to almost 158 million, resulting in 20 240 664 extra cases with current trends using base case estimates in parallel with an estimated growth in females from 3·34 billion to 4·181 billion. In high-income countries, the economic burden from lost productivity could be up to US$14·39 billion annually. The high prevalence, substantial morbidity, and economic losses of recurrent vulvovaginal candidiasis require better solutions and improved quality of care for affected women.

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Introduction

Surveys suggest that about 75% of women develop vulvovaginal candidiasis (thrush or yeast infection) at least once in their lifetime.[1] The infection can be triggered by various factors such as courses of antibiotics or new sexual partners, but most episodes have no identifiable trigger. The infection is more common in pregnancy, after treatment with antibiotics, and in women taking hormone replacement therapy (HRT; figure 1). HIV-infected women have the same incidence as non-HIV-infected women. Diagnosis of vulvovaginal candidiasis is established by a combination of microscopic examination showing yeasts, hyphae, culture, or a combination of all from a vulval or vaginal swab in the presence of compatible clinical signs and symptoms.[2] The most common pathogen is *Candida albicans*, but several non-albicans *Candida* species can cause symptoms.[3]

Vulvovaginal candidiasis usually responds rapidly to topical or oral antifungal therapy, but a chronic subtype has recently been described.[4,5] However, some women develop recurrent vulvovaginal candidiasis, which is arbitrarily defined as four or more episodes every year. Suppressive therapy is used in these patients, which normally provides full resolution of symptoms for the duration of the treatment. After withdrawal of suppressive therapy, most patients have only occasional episodes; however, many others need another period of suppressive therapy and often for prolonged durations.

The severity of symptoms in women with recurrent vulvovaginal candidiasis varies from moderate to severe, but invariably affects quality of life and is associated with considerable stress.[6–11] In addition to pruritus, soreness, and discomfort (appendix p 4), women with recurrent vulvovaginal candidiasis often report loss of confidence and self-esteem, inability to carry on with their normal physical activities, and difficulties with their sexual life and intimate relationships. Reports of feeling "dirty" and suspicions about sexually transmitted infection acquired from their partner are almost universal.[8] Male partners can develop penile irritation, consequent to vulvovaginal candidiasis.[12] Many assumed causes are identified and corrected (such as change in underwear, douches, dietary adjustment, or change in contraception) and therapies tried, but most with little success.

The treatment market includes antifungal pessaries and single (fluconazole) or two-dose (itraconazole) oral therapy.[10] A large number of different topical azoles are sold, many generic, with good efficacy for single-episode vulvovaginal candidiasis. The estimated global market is US$600 million for gynaecological products and includes $257 million of sales of the market leader Canesten (clotrimazole; Bayer, Leverkusen, Germany) in 2013, most of which was for vulvovaginal candidiasis.[13] A substantial proportion of the sales of fluconazole ($242 million in 2013) and itraconazole ($350 million in 2011) are for vulvovaginal candidiasis.[14] It is not possible to separate out the vulvovaginal candidiasis and recurrent vulvovaginal candidiasis market segments.

No global estimate of the prevalence of recurrent vulvovaginal candidiasis has previously been reported and several factors could increase its frequency in coming decades. The pathogenesis of the disease is poorly understood,[3,10] and might partly have a genetic basis.[15,16] Azole resistance in *C albicans* has now been described in women with vulvovaginal candidiasis[17–19] and replacement of *C albicans* by the fluconazole-resistant *Candida glabrata* is frequently recognised. Drivers for increased rates of vulvovaginal candidiasis are an ageing but sexually active population using HRT,[20] antibiotic misuse, and increased numbers of patients with

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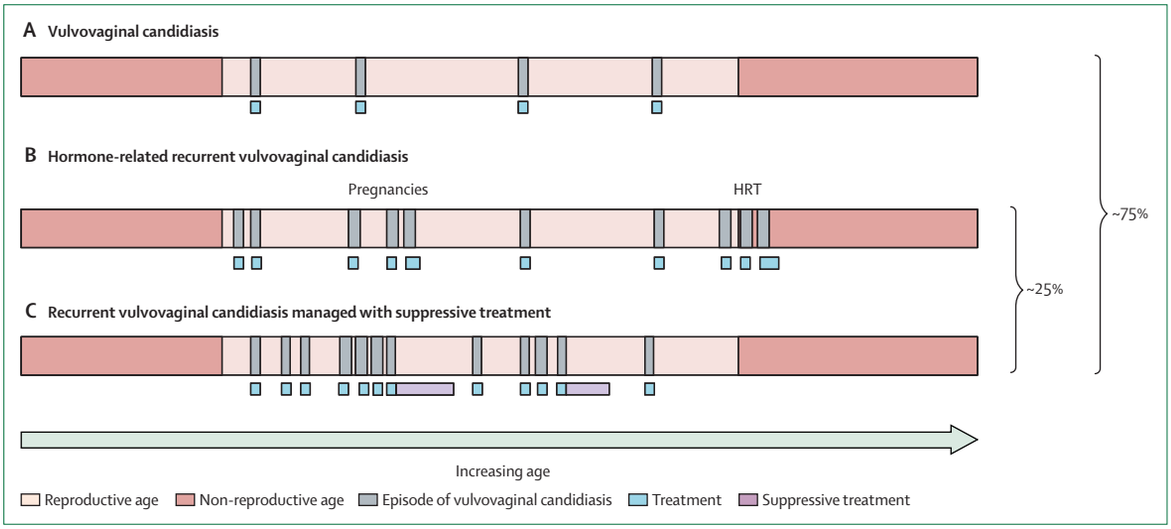

Figure 1: **Patterns of vulvovaginal candidiasis**
(A) Uncomplicated vulvovaginal candidiasis during reproductive life (approximate 75% lifetime risk[1]). (B) Vulvovaginal candidiasis triggered by hormonal changes—eg, puberty, pregnancy, menopause, or use of hormonal contraception or hormone replacement therapy (HRT). (C) Recurrent vulvovaginal candidiasis in healthy women without risk factors (approximate 25% lifetime risk [calculated in this Review]).

predisposing conditions such as diabetes treated with sodium-glucose cotransporter-2 (SGLT2) inhibitors.[21] The lifetime experience of women with vulvovaginal candidiasis is not well documented and single point-in-time surveys usually only capture the current prevalence of recurrent vulvovaginal candidiasis, not lifetime experience, with few studies[22,23] exploring economic impact and none since 2000. Thus, we did a systematic review to estimate the global prevalence, lifetime incidence, and future impact of recurrent vulvovaginal candidiasis up to 2030, and likely economic impact.

Methods

Search strategy and selection criteria

For more on **GRADE** see http://www.gradeworkinggroup.org/

This systematic review adheres to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[24] One author (MK) searched the PubMed, Embase, and Web of Science databases for published and unpublished or hidden works from Jan 1, 1985, to Feb 28, 2016 (and updated the search on Oct 31, 2016), for population-based studies on the prevalence of recurrent vulvovaginal candidiasis, with the British Society for Medical Mycology recommended search terms "(vulvovaginal candidiasis, vaginal candidosis, vaginal candida)", combined with "(epidemiology OR prevalence)". In addition, we searched Embase with the term "exp vagina candidiasis/ep". Full search terms are listed in the appendix (p 1). Inclusion criteria were population-based studies reporting the prevalence of recurrent vulvovaginal candidiasis (defined as at least four episodes every year) in a defined population with either a confirmed microbiological diagnosis of vulvovaginal candidiasis or self-diagnosis (using treatment as a proxy). Identified papers were confirmed by two other authors (RR-R and DWD). We also searched reference lists of retrieved articles. Papers in all languages with an English abstract were included.

We excluded studies that referred to selected populations (eg, sexually transmitted disease clinics), discussed colonisation or sporadic vulvovaginal candidiasis only, or that were not available online or through the library. Eligibility of papers was assessed by full-text review by MK and confirmed by two other authors (RR-R and DWD). To estimate global prevalence of recurrent vulvovaginal candidiasis, we included only papers that reported rates of this disease with a general population denominator as distinct from those seeking medical help. We assessed papers using modified GRADE criteria and discarded those with a GRADE score of 1 or lower (appendix pp 2–3).[25] Because GRADE is primarily designed for assessment of clinical trials, we made the following modifications for this analysis: for the consistency domain, we assessed degree of consistency of incidence instead of consistency of effect, and for the effect size domain, we assessed population size (0, <500; +1, 500–5000; +2, >5000).

Data extraction and prevalence calculations

Two authors extracted prevalence data from included papers (MK and RR-R). We then obtained population data by country and stratified age from the UN World Population Prospects 2012 database and used medium-fertility population growth statistics from this database to estimate the likely global burden of recurrent vulvovaginal candidiasis in 2012, and also extrapolated this to 2030, based on population growth of women aged 15–54 years.[26] We derived global estimates of recurrent vulvovaginal candidiasis for four different age bands (15–24 years,

25–34 years, 35–44 years, 45–54 years) using the most recent multicountry estimate from the largest multicountry study with unbiased sampling.[27] Our base case assumption was 75% of these estimates to allow for incorrect self-diagnosis, a well recognised problem with vulvovaginal candidiasis,[28–31] with sensitivity analyses with lower (–25%) and upper (+25%) bounds of the multicountry data. We calculated the estimated prevalence of recurrent vulvovaginal candidiasis per 100 000 females (ie, all ages) in each country.

To provide an alternative estimate, we estimated annual prevalence of recurrent vulvovaginal candidiasis per 100 000 females using a flat 6% estimate across each age band per country, derived from Foxman and colleagues' pooled prevalence estimate of 9%,[27] which we reduced to take into account likely inaccuracy of self-diagnosis. To calculate the 9% pooled prevalence estimate, we included only studies with unbiased populations and microbiological diagnosis of recurrent vulvovaginal candidiasis. We grouped women with recurrent vulvovaginal candidiasis alongside those with chronic vulvovaginal candidiasis, because chronic disease is not fully accepted as clinically distinct from recurrent disease and we were unable to separate the two types in most of the identified studies. We applied the same calculations to the UN medium-fertility projections for population to estimate the future impact of recurrent vulvovaginal candidiasis up to 2030. We estimated lifetime incidence based on the data provided by Foxman and colleagues.[27]

There are no published estimates of the productivity losses associated with vulvovaginal candidiasis or recurrent vulvovaginal candidiasis. We therefore calculated annual productivity losses for 2010 on the basis of data from Aballéa and colleagues,[6] the most recent multicountry estimate, in which the monetary equivalence of the annual productivity loss had been estimated for the UK, France, Spain, Italy, Germany, and the USA by use of 2010 World Bank data. The assumptions made are described in the appendix (p 3). All analyses were done in Excel (version 14.5.6 [2011 for Mac]).

Results

Our searches identified 1052 records, of which 489 were unique articles (figure 2). 442 articles were not considered relevant after title and abstract screening, or were not available for analysis, leaving 47 full manuscripts to be assessed for eligibility. 39 articles were excluded because they were unrelated to epidemiology, provided no usable data, were of poor methodological quality, or did not assess prevalence of recurrent disease. Eight articles with robust denominator data and diagnosis or other objective indicator of vulvovaginal candidiasis were included for detailed analysis (see appendix p 2).[12,22,27,32–36] These studies consisted of a total of 17 365 patients from 11 countries.

Our base case was based on the largest unbiased study done in six countries.[27] In this study, a telephone survey in 6000 women in the USA, France, Germany, Italy, Spain, and the UK found that 540 (9%) women had recurrent vulvovaginal candidiasis with some variation by age and country (table 1). The seven other selected articles support this base case. A prospective study in asymptomatic women aged 18–30 years, in which vaginal sampling and questionnaires were done at four timepoints over 36 months, showed that 496 (70%) of 709 women had *Candida* spp by culture at one timepoint, and 26 (4%) had it at all four timepoints.[32] In a small family practice study in Melbourne, Australia, of 76 control women who completed a health questionnaire, two (3%) reported that they had recurrent vulvovaginal candidiasis monthly and another two (3%) reported that they had vulvovaginal candidiasis "almost all the time".[33] 1117 women aged 18–70 years (86% response rate) from five general practices in Melbourne reported vulvovaginitis by questionnaire: 798 (73%) of 1089 reported ever having an episode and more than 7% had four or more episodes in the past year.[34] A larger survey in the USA found that 160 (8%) of 2000 women contacted through random telephone digit-dialling had four or more episodes of vulvovaginal candidiasis in the previous 12 months.[22] In eight cities in Italy, of 1138 women attending gynaecological clinics for any condition, 77 (10%) of 767 evaluable patients had a history of recurrent vulvovaginal candidiasis, with a mean number of

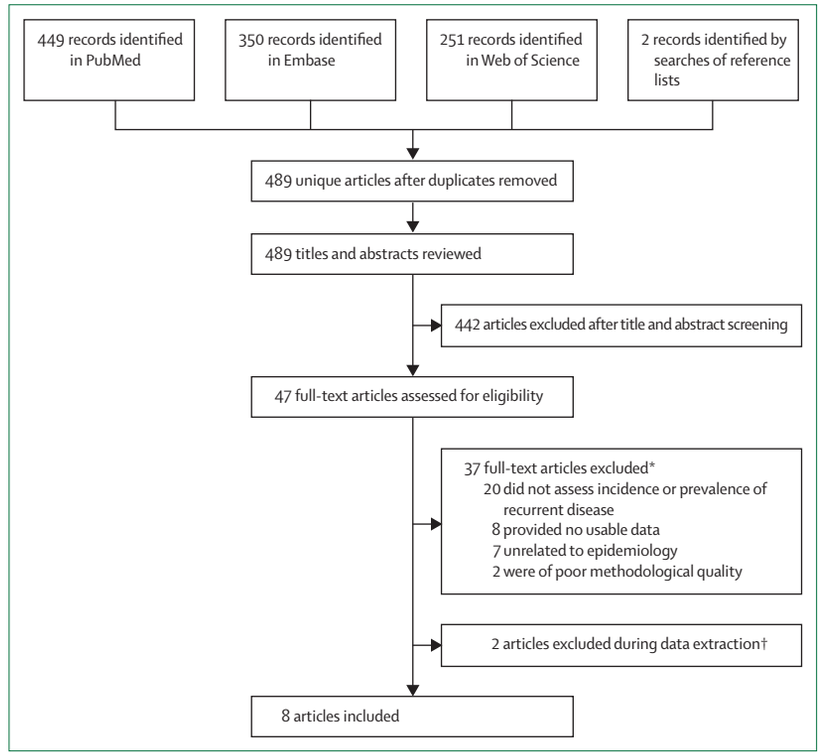

Figure 2: **Literature search and study selection**
*The reasons for exclusion were usually multiple, but the most common was a lack of a suitable denominator to assess prevalence. The main criterion for exclusion is listed. †Two articles were excluded because the translation from a foreign language made it clear that they did not fulfil the diagnostic criteria for recurrent vulvovaginal candidiasis or did not have an appropriate denominator, or both.

	15–24 years	25–34 years	35–44 years	45–54 years	15–54 years
Global female population (2012)	595 454 000	572 804 000	468 421 000	381 388 000	1 968 068 000
Prevalence (%)	5·39%	9·00%	7·64%	5·95%	7·00%
Estimated prevalence (base case)	32 095 000	47 052 000	35 387 000	22 693 000	137 627 000
Base case +25%	40 012 000	58 082 000	44 073 000	28 037 000	172 034 000
Base case –25%	24 007 000	35 029 000	26 084 000	17 002 000	103 220 000

Table 1: **Age-specific prevalence of self-reported recurrent vulvovaginal candidiasis from a survey of 6000 women in six countries and global prevalence by 10-year age group[27]**

6·8 episodes in 12 months, of which 91% were not medically confirmed.[12] In an online survey in the USA and five European countries of 6010 women's experiences of and attitudes towards vulvovaginal candidiasis and bacterial vaginosis, 1945 provided full responses and 875 (44%) women thought that they had had an episode of vulvovaginal candidiasis, of whom 175 (20%) had one episode, 394 (45%) had two to five recurrences, 254 (29%) had five to 20 episodes, and 53 (6%) had more than 20 episodes.[35] Among 495 randomly selected Turkish women attending a gynaecology clinic, 53 (11%) reported current recurrent vulvovaginal candidiasis and 98 (20%) a history of recurrent vulvovaginal candidiasis.[36]

Since our base case is based on self-reported vulvovaginal candidiasis, we used an annual prevalence of 75% of the estimates to allow for incorrect self-diagnosis, a well recognised problem with vulvovaginal candidiasis,[28–31] with sensitivity analyses with lower (–25%) and upper (+25%) bounds of the multicountry data. Our base case also stratified the estimates by 10-year age group, and as an alternative approach we used a flat 6% rate across all age groups.

Using our base case, we estimated that 137 627 000 (range 103 221 000–172 034 000) women worldwide are affected by recurrent vulvovaginal candidiasis, with a global annual prevalence of 3871 per 100 000 females (table 2). The group with the highest prevalence was women aged 25–34 years, with an estimated 47 052 000 affected (35 289 000–58 815 000; table 2). As expected, numbers were highest in the most populous countries (table 2), but also reflected country sex demographics (figure 3). Base case estimates of recurrent vulvovaginal candidiasis in the female population varied from as low as 2990 and 3063 per 100 000 in Timor-Leste and Niger, respectively, to 5580 per 100 000 in the United Arab Emirates, reflecting female population demographics. Using the alternative, flat 6% model, we derived a total of 118 084 000 women affected by recurrent vulvovaginal candidiasis worldwide.

Using medium-fertility population growth statistics from the UN World Population Prospects 2012 database, we estimated the likely global burden of recurrent vulvovaginal candidiasis to 2030. The UN estimates that the female population will grow from 3·4 billion to 4·181 billion between 2012 and 2030. By 2030, the population of women with recurrent vulvovaginal candidiasis each year is estimated to increase to almost 158 million, resulting in 20 240 664 extra cases with current trends using base case estimates (appendix p 4), or by 17 million using the flat 6% scenario (appendix p 5).

Foxman and colleagues[27] obtained data on the duration of symptoms of recurrent vulvovaginal candidiasis, linked with age, for 2471 women. Most women reported the duration of recurrent vulvovaginal candidiasis to be 1–2 years, although a minority had symptoms for 4 or 5 years, and some for longer. By the age of 50 years, 618 (25%) of 2471 women had had recurrent vulvovaginal candidiasis. Applying this figure to the estimated 1·968 billion women aged 15–54 years alive in 2012,[28] 372 million would have had or were living with recurrent vulvovaginal candidiasis.

Based on our base case estimates and the amount of time off work in high-income countries (33 hours per year),[37] annual hours actually worked, and average annual female wages in these countries, we estimated the total annual lost productivity to be $14·39 billion in 2010, even when 47 countries or territories were excluded because of a lack of available data. Estimates of lost productivity for individual countries are given in the appendix (p 6).

Discussion

On the basis of this systematic review, recurrent vulvovaginal candidiasis probably affects more than 130 million women in any given year, with a global annual prevalence of 3871 per 100 000 females. This figure lies on a similar scale to the 300 million people estimated to have depression, 200 million adults with asthma, and 199 million women with premenstrual syndrome.[38] We have predicted more than 20 million extra cases of recurrent vulvovaginal candidiasis by 2030. The vast majority of the increased world population in 2030 is expected to live in developing countries,[27] potentially exacerbating the impact of an increased burden of this disease, in view of frequent imprecise diagnosis, incorrect empirical therapy, unaffordable or inaccessible antifungal therapy, and the emergence of azole-resistant *Candida* spp causing recurrent vulvovaginal candidiasis.

Recurrent vulvovaginal candidiasis and its chronic subtype are syndromes that might or might not be pathogenetically or clinically distinct, and they probably represent a continuum of vaginal response to *Candida* spp. For estimation purposes, we attempted to estimate the incidence of chronic vulvovaginal

	Female population	Females aged 15–54 years	Flat 6% case burden	6% case prevalence per 100 000 females	Base case burden	Base case –25%	Base case +25%	Base case prevalence per 100 000 females
Worldwide	3 430 235 000	1 968 068 000	118 084 000	3323	137 627 000	103 220 000	172 034 000	3871
China	655 638 000	416 867 800	25 012 000	3815	29 082 000	21 812 000	36 353 000	4436
India	581 881 000	337 674 000	20 261 000	3482	23 630 000	17 723 000	29 538 000	4061
USA	158 718 000	86 125 000	5 168 000	3256	5 992 000	4 494 000	7 490 000	3775
Indonesia	119 589 000	70 591 000	4 235 000	3542	5 003 000	3 753 000	6 254 000	4184
Brazil	99 109 000	59 283 000	3 557 000	3589	4 185 000	3 139 000	5 232 000	4223
Pakistan	84 223 000	47 167 000	2 830 000	3360	3 260 000	2 445 000	4 075 000	3871
Nigeria	78 512 000	38 564 000	2 314 000	2947	2 676 000	2 007 000	3 345 000	3409
Russia	77 263 000	44 012 000	2 641 000	3418	3 077 000	2 308 000	3 846 000	3982
Bangladesh	74 391 000	44 206 000	2 652 000	3565	3 110 000	2 332 000	3 887 000	4180
Japan	65 317 800	30 894 000	1 854 000	2838	2 193 000	1 645 000	2 741 000	3357
Mexico	60 843 000	35 536 000	2 132 000	3504	2 495 000	1 871 000	3 118 000	4100
Philippines	46 599 000	25 836 000	1 550 000	3327	1 795 000	1 346 000	2 244 000	3853
Vietnam	45 077 000	28 269 000	1 696 000	3763	1 976 000	1 482 000	2 470 000	4384
Ethiopia	43 530 000	21 124 000	1 267 000	2912	1 454 000	1 090 000	1 817 000	3340
Germany	42 342 000	21 977 000	1 319 000	3114	1 532 000	1 149 000	1 915 000	3619
Egypt	38 869 000	21 812 000	1 309 000	3367	1 518 000	1 138 000	1 897 000	3905
Iran	36 806 000	24 131 000	1 448 000	3934	1 704 000	1 278 000	2 130 000	4630
Turkey	36 701 000	21 564 000	1 294 000	3525	1 523 000	1 142 000	1 903 000	4149
Thailand	33 849 000	20 911 000	1 255 000	3707	1 475 000	1 106 000	1 844 000	4358
France	32 656 000	16 573 000	994 000	3045	1 157 000	867 800	1 446 000	3543
UK	31 544 000	16 708 000	1 002 000	3178	1 169 000	877 000	1 461 000	3707
DR Congo	31 301 000	14 974 000	898 000	2870	1 030 000	773 000	1 288 000	3292
Italy	31 149 000	16 066 000	964 000	3095	1 137 000	853 000	1 421 000	3650
Myanmar	26 731 000	16 614 000	997 000	3729	1 176 000	882 000	1 470 000	4400
South Africa	26 500 000	15 255 000	915 000	3454	1 063 000	798 000	1 329 000	4013
Ukraine	24 804 000	13 662 000	820 000	3305	957 000	718 000	1 197 000	3860
South Korea	24 346 000	14 844 000	891 000	3658	1 047 000	785 000	1 309 000	4301
Colombia	23 591 000	13 845 000	831 000	3521	970 000	727 000	1 212 000	4110
Spain	23 381 000	12 891 000	773 000	3308	926 000	695 000	1 158 000	3961
Tanzania	22 498 000	10 805 000	648 000	2882	748 000	561 000	935 000	3323
Argentina	20 621 000	11 258 000	675 000	3276	792 000	594 000	989 000	3839
Kenya	20 492 000	10 476 000	629 000	3067	728 000	546 000	910 000	3554
Poland	19 749 000	11 045 000	663 000	3356	780 000	585 000	975 000	3950
Algeria	18 320 000	11 430 000	686 000	3743	807 000	605 000	1 009 000	4404
Sudan	17 764 000	9 042 000	543 000	3054	628 000	471 000	786 000	3538
Canada	17 200 000	9 614 000	577 000	3354	670 000	503 000	838 000	3897
Uganda	16 952 000	7 741 000	464 000	2740	531 000	399 000	664 000	3135
Morocco	16 088 000	9 842 000	591 000	3671	690 000	518 000	863 000	4291
Iraq	15 299 000	7 880 000	473 000	3090	550 000	412 000	687 000	3594
Peru	14 597 000	8 407 000	504 000	3456	589 000	441 000	736 000	4032
Malaysia	14 539 000	8 894 000	534 000	3670	622 000	467 000	778 000	4281
Venezuela	14 468 000	8 384 000	503 000	3477	587 000	440 000	733 000	4056
Afghanistan	13 983 000	6 396 000	384 000	2744	439 000	329 000	549 000	3139
Uzbekistan	13 955 000	8 478 000	509 000	3645	586 000	440 000	733 000	4201
Nepal	13 751 000	7 462 000	447 800	3256	518 000	388 000	647 000	3765
North Korea	12 531 000	7 422 000	445 000	3554	519 000	389 000	648 000	4139
Mozambique	12 288 000	5 908 000	354 000	2885	408 000	306 000	511 000	3324
Ghana	12 256 000	6 607 000	396 000	3234	462 000	346 000	577 000	3766
Saudi Arabia	11 866 000	6 948 000	417 000	3513	494 000	371 000	618 000	4166
Yemen	11 283 000	5 832 000	350 000	3101	398 000	298 000	497 000	4407

Table 2: **Number of women with recurrent vulvovaginal candidiasis and annual global prevalence per 100 000 females in the 50 most populous countries (by females), using base case estimates and a flat 6% rate**

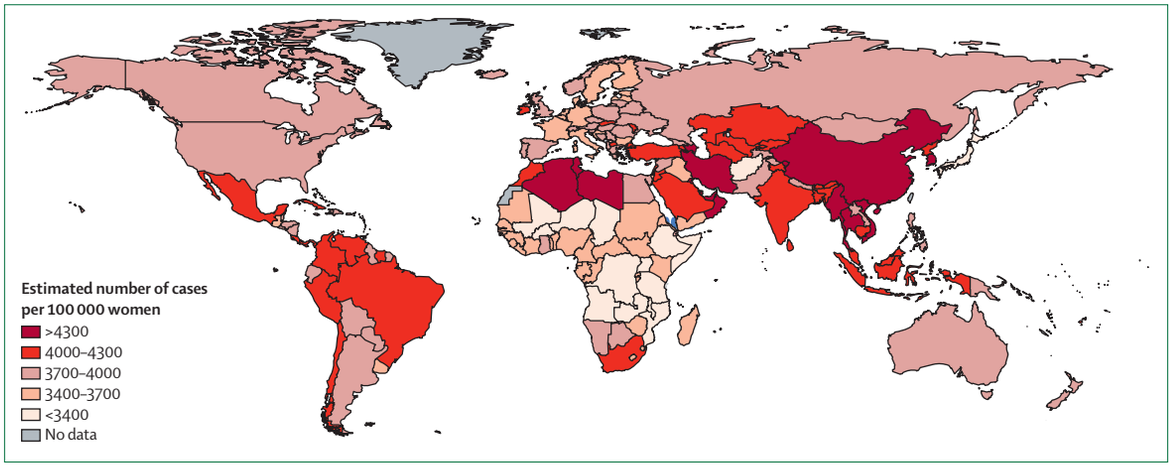

Figure 3: **Global prevalence of recurrent vulvovaginal candidiasis per 100 000 women (in 2013)**
Estimated using the 6% flat rate for women 15–54 years of age. Prevalence primarily reflects the variable demographics of women in their reproductive years globally.

candidiasis, but the ratios provided in the published work are quite variable, and strict diagnostic criteria have not been applied. In a report by Sawyer and colleagues,[33] a similar proportion of women reported having vulvovaginal candidiasis monthly (3%) or almost all the time (3%). In the recent study by Foxman and colleagues,[27] 28 (5%) of 536 women with recurrent vulvovaginal candidiasis reported 8 or more years of disease and 66 (12%) reported 5 or more years, which could reflect intermittent or semi-continuous symptoms. If the assumption that 12% approximates to the subpopulation of chronic vulvovaginal candidiasis, this equates to 16 928 000 (range 12 696 000–21 160 000) women with chronic or recurrent vulvovaginal candidiasis, or both, for 5 years or more. No comparative age-specific information for recurrent vulvovaginal candidiasis or chronic vulvovaginal candidiasis has been published. This supposition needs further study.

The estimated global burden of recurrent vulvovaginal candidiasis is high, but given the changing age structure of the global female population and prevalence of diseases that increase risk for vulvovaginal candidiasis, it is likely to increase. As populations age and remain reasonably healthy, sexual activity also extends into middle and old age. The use of HRT is increasingly common (global market is projected to exceed $3·3 billion by 2020), partly to alleviate menopausal symptoms and partly to improve sexual experience. Increased sexual adventurousness in the over 50s is leading to increasing sexually transmitted disease and presumably vulvovaginal candidiasis.[39] The new anti-diabetic agents SGLT2 inhibitors (dapagliflozin and canagliflozin), which increase glycosuria, also increase episodes of vulvovaginal candidiasis.[21,40,41] In view of the large number of people with non-insulin-dependent diabetes worldwide (>300 million), the number of cases of vulvovaginal candidiasis is set to rise. Women with cystic fibrosis are also frequently affected and living longer.[33,42,43] Antibiotic use increases the rate of vulvovaginal candidiasis—by 23% in one questionnaire study of vulvovaginitis,[34] which is caused by *Candida* spp in more than 90% of cases.[44] Therefore, the prevalence of recurrent vulvovaginal candidiasis is more likely to increase than decrease in the future.

There is a small peak of recurrent vulvovaginal candidiasis in postmenopausal women taking HRT, assumed to be 55 years or older.[20,45] A surprisingly large number of postmenopausal women are affected. In a study of women aged 62·5 years from a private practice in Australia, culture-positive clinical vulvovaginal candidiasis was found in 70 (49%) women on HRT compared with 79 (1%) women who were not on HRT.[20] Most women with vulvovaginal candidiasis who were taking HRT had a history of the infection (23 [68%] of 34) before menopause. The risk of vulvovaginal candidiasis seemed to be similar in those taking systemic and local HRT. However, it is not possible to estimate the global number of postmenopausal women with vulvovaginal candidiasis because the absolute risk of vulvovaginal candidiasis in women taking oral or vaginal oestrogen replacement has not been determined, the rates of HRT use vary substantially in different high-income countries, and HRT is used less frequently in low-income and lower middle-income countries.[46] Careful study of the inter-relationship between HRT and vulvovaginal candidiasis and its impact on quality of life is required.

Vulvovaginal candidiasis is a common reason for medical, nursing, and pharmacist consultation. Before the availability of over-the-counter antifungal treatment in the USA, approximately 13 million cases of vulvovaginal candidiasis annually accounted for 10 million visits to the gynaecologist.[47] In 1995 in the USA, medical costs for vulvovaginal candidiasis were estimated to be $1·8 billion, with approximately 50% related to doctor visit costs.[22] With the advent of over-the-counter treatments, this cost is likely to have fallen, but there are no recent estimates.

Most women with physician or self-diagnosed vulvovaginal candidiasis use expensive oral and occasionally vaginal probiotics in the absence of data confirming therapeutic benefit. No estimates of the direct health-care and treatment costs of recurrent vulvovaginal candidiasis exist, but they are likely to be substantial.

True population-based studies on recurrent vulvovaginal candidiasis are rare. Remarkably few studies have been done in unselected populations of women, and almost all have been in women attending a gynaecologist or sexually transmitted disease clinic with vaginal symptoms, and therefore tend to exaggerate the frequency of vulvovaginal candidiasis and recurrent vulvovaginal candidiasis. Also, many studies rely on self-diagnosis and reporting. Recurrent vulvovaginal candidiasis and recurrent episodes of bacterial vaginosis are often confused by affected women. Many other genital conditions such as inflammatory dermatological conditions of the vulva including lichen sclerosus, vulvar vestibulitis syndrome, desquamative inflammatory vaginitis, vulvar dermatoses, contact dermatitis, and physiological leucorrhoea are also often mistaken for vulvovaginal candidiasis, and these are the primary reasons we reduced our base case estimate to 75% of the self-reported figure. Diagnosis of other common infections and other disorders, notably bacterial vaginosis, is often made without clinical examination or microscopy, creating an intrinsic weakness of our estimates. We do not believe that a truly robust community estimate of sufficient scale is experimentally achievable, unless point-of-care testing by women is possible and reliable. At present, women would have to be studied carefully for at least 12 months and any symptoms would require a diagnostic assessment with the combination of clinical examination, microscopy, and culture; many women would not volunteer for such a study.

There are several assumptions in our estimates. The most profound is that recurrent vulvovaginal candidiasis affects women with equal frequency in all populations, which is highly unlikely to be the case, even if present in all populations. In Europe and North America, variation in prevalence of self-reported recurrent vulvovaginal candidiasis was present within regions of Spain, Italy, and the USA.[27] A survey of bacterial vaginosis in teenagers in Ecuador found a remarkably high prevalence compared with that in Europe,[48] suggestive of substantial population variation of vulvovaginal candidiasis. With respect to the economic estimates, we have assumed that all women with recurrent vulvovaginal candidiasis are working, because clinically they are likely to have the disease between 15 and 54 years of age. We also assumed that workers and those not working in paid employment have an equal risk of recurrent vulvovaginal candidiasis. Because working women older than 54 years of age are included in some of the national economic estimates, there could be a small overestimation of equivalent productivity loss in women older than 55 years. However, some of these older women will have recurrent vulvovaginal candidiasis, which we have been unable to model accurately, reducing the overestimation of economic loss. We did not use a multiplier to account for additional company losses as with other studies,[49,50] which means our figure is likely to be an underestimate of overall loss due to time off work for recurrent vulvovaginal candidiasis. Finally, our economic estimates are based entirely on data from 2010. As we predict a rise in the affected population, the true cost of recurrent vulvovaginal candidiasis is likely to rise.

Recurrent vulvovaginal candidiasis can be controlled by long-term suppressive antifungal therapy but cure is usually elusive,[10,51] unless the condition remits. An exploratory randomised controlled vaccine study has recently been completed (NCT01926028) after findings of long-lasting protection in rats with a different preparation and human safety data.[52,53] Vaccine efficacy was partial, particularly in those younger than 40 years of age.[54] Should this vaccine prove its worth clinically, this would provide a major benefit to affected women.

Despite its limitations, our systematic review provides a comprehensive assessment of the prevalence of recurrent vulvovaginal candidiasis and an estimate of the worldwide prevalence of the disease. Recurrent vulvovaginal candidiasis is a debilitating, long-term condition in women and its prevalence has been poorly documented across the world. The pathogenesis of the disease is poorly understood and, in view of its impact on women's health, requires better solutions than are currently available. Some patients at greatest risk are well known: women with diabetes; women requiring frequent antibiotics, usually for relapsing chest or urinary infections; women with cystic fibrosis; and those with a history of frequent episodes of vulvovaginal candidiasis. These women need better information and support, combined with suppressive antifungal therapy. In the future, genetic testing may identify those most at risk and needing alternative management strategies. Resistance to fluconazole and other azoles requires alternative therapy, usually nystatin or boric acid pessaries, and these need to be accessible and affordable. Because the symptoms of bacterial vaginosis and vulvovaginal candidiasis are similar, a rapid, point-of-care test to distinguish between the two would be of great value in treatment decision making. Azole resistance can probably be addressed with such an approach, with potential for minimising the impact of oral triazole resistance, and allowing successful suppressive therapy. For women with resistant infections, alternative antifungal therapies are on the horizon.[55] Improvement of women's health is a realistic target if the problem of recurrent vulvovaginal candidiasis is addressed.

Contributors

DWD conceived the project, wrote the first draft of the report, and contributed to revisions. MK did the literature modelling and literature searches, and contributed to writing of the report. JDS contributed to the

criteria for paper acceptance, and to key assumptions underlying the paper's conclusions, provided figure S1 in the appendix, and contributed to drafting and redrafting of the report. RR-R contributed to the design of the systematic review, contributed to writing of the report, evaluated published papers and abstracts, conceived figure 1, and addressed all of the revisions.

Declaration of interests

DWD and family hold founder shares in F2G, a University of Manchester spin-out antifungal discovery company. He acts or has recently acted as a consultant to Astellas, Sigma-Tau, Basilea, Scynexis, Cidara, Biosergen, Quintiles, Pulmatrix, Pulmocide, and Zambon; and has received grants from Pfizer, Gilead, MSD, and Astellas. In the past 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Mylan, Merck, and Pfizer. All other authors declare no competing interests.

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