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**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 global estimate of the prevalence or lifetime burden of this disease has 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 females; 492 million women are affected by recurrent vulvovaginal candidiasis over their lifetime. The 25–34-year age group has the highest prevalence at 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 parallel with a an estimated growth in females from 3,340 to 4,181. 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**

**Introduction [h2]**

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 and/or culture 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.6–10 In addition to pruritus, soreness, and discomfort (Suppl Figure SI), 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.11 Many assumed causes are identified and corrected (such as with a change in underwear, douches, dietary adjustment, or change in contraception) and therapies tried, but most with little success. Quiet desperation is common amongst those most severely affected.­­­

The treatment market includes antifungal pessaries and single (fluconazole) or two-dose (itraconazole) oral therapy.12 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) sales 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 may increase its frequency in coming decades. but it is predicted to rise. Its pathogenesis is poorly understood3, and may partly have a genetic basis. Azole resistance in *C. albicans* has now been described in women with VVC and replacement of *C. albicans* by the fluconazole-resistant *C. glabrata* is frequently recognized. Drivers for increased rates of vulvovaginal candidiasis are an ageing but sexually active population using HRT,15 antibiotic misuse, and increased numbers of patients with predisposing conditions such as diabetes treated with sodium-glucose cotransporter-2 (SGLT2) inhibitors.16 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. We did a systematic review to estimate the global prevalence, lifetime incidence, and future impact of recurrent vulvovaginal candidiasis to 2030, and likely economic impact.

**Methods [h2]**

**Search strategy and selection criteria [h3]**

This systematic review adheres to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.17 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. 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 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 and DWD). To estimate global rVVC prevalence, we included only papers that reported rates of recurrent vulvovaginal candidiasis 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 (SupplTables S1 and S2).18 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 [h3]**

Two authors extracted prevalence data from included papers (MK,). 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. 19 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 and the largest multicountry study with unbiased sampling.20 Our base case assumption was 75% of these estimates to allow for incorrect self-diagnosis, a well recognised problem with vulvovaginal candidiasis,21–24 with sensitivity analyses with lower (–33%) and upper (+33%) bounds of the multicountry data. We calculated the estimated prevalence of recurrent vulvovaginal candidiasis per 100 000 women in each country. To provide an alternative estimate, we estimated annual prevalence of recurrent vulvovaginal candidiasis per 100 000 women using a flat 6%, derived from the Foxman pooled prevalence estimate of 9%20, which we reduced to take into account likely inaccuracy of self-diagnosis. 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.20

There are no published estimates of the productivity losses associated with vulvovaginal candidiasis or recurrent vulvovaginal candidiasis. We therefore calculated annual productivity losses on the basis of data from Aballéa and colleagues,[6](#_ENREF_4) 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. The assumptions made are described in the appendix .

**Results [h2]**

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. Eight articles with robust denominator data and diagnosis or other objective indicator of vulvovaginal candidiasis were included for detailed analysis (see appendix).11,20,25–30 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.20 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 of 709 (70%) women had *Candida* spp by culture at one timepoint, and 26 (4%) had it at all four timepoints.25 In a small family practice study in Melbourne, Australia, of 76 control women who completed a health questionnaire, 2 (3%) reported that they had recurrent vulvovaginal candidiasis monthly and another 2 (3%) reported that they had vulvovaginal candidiasis “almost all the time”.30 1117 women aged 18–70 years (86% response rate) from five general practices in Melbourne reported vulvovaginitis by questionnaire: 1089 (73%) reported ever having an episode and XX (7%) had four or more episodes in the past year.29 A larger survey in the USA found that 160 (8%) of 2000 women randomly contacted through random telephone digit-dialling had four or more episodes of vulvovaginal candidiasis in the previous 12 months.26 In eight cities in Italy, of 1138 women attending gynaecological clinics for any condition, 77 of 767 evaluable patients (10%) had a history of recurrent vulvovaginal candidiasis, with a mean number of 6.8 episodes in 12 months, 91% not medically confirmed.11 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.28 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.27 Additional non-selected studies also supported this base case assumption. In a partial population study of 650 women in two villages in rural India, vaginal discharge was found in 8·3–13·5% of women and *Candida* spp seen or grown in 190 (29%).31 Of 163 sex workers in Spain, 12 (7%) reported recurrent vulvovaginal candidiasis, with all diagnoses supported microbiologically at least once.32 By use of a definition of three or more episodes for recurrent disease, but without a timeframe, another study at an adolescent centre in Sweden showed a prevalence of recurrent vulvovaginal candidiasis of 22% (45 of 207).33

As our base case is based on self-reported VVC, we used an annual prevalence of 75% of the estimates to allow for incorrect self-diagnosis, a well-recognized problem with VVC, 21-24 with sensitivity analyses of ±33% of the multi-country data. Our base case also stratified the estimates by decile, and as alternative approach we used a flat 6% rate across all age groups.

Using our base case, we estimated that 137 627 332 (range 103 220 499–172 034 165) women worldwide are affected by recurrent vulvovaginal candidiasis, 3871 per 100 000 women (Table 2). The group with the highest prevalence was women aged 25–34 years, with an estimated 47 052 378 affected (35 289 283–58 815 472; figure 3). As expected, numbers were highest in the most populous countries (table 2), but also reflected country sex demographics (figure 4). 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 ,082 ,404 affected 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 (appendix). By 2030, the population of women with recurrent vulvovaginal candidiasis is estimated to increase to almost 158 million, resulting in 20 240 664 extra cases with current trends using base case estimates (supplFig 2), or by 17 million using the flat 6% scenario (SupplFig3).

Foxman and colleagues20 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, 1500 (25%) women globally had had recurrent vulvovaginal candidiasis. Applying this figure to the estimated 1968 billion women aged 15–54 years alive in 201219, 492 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),34 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 SupplTable 3 ~~(or Appendix Table S3)~~.

**Discussion [h2]**

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.35 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,20 potentially exacerbating the impact of an increased burden of this disease, given frequent imprecise diagnosis, incorrect empirical therapy, unaffordable or inaccessible antifungal therapy and the emergence of azole resistant *Candida* spp. causing rVVC.

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 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,30 a similar proportion of women reported having vulvovaginal candidiasis monthly or almost all the time (3% each). In the recent study by Foxman and colleagues,20 28 (5%) of 536 women with recurrent vulvovaginal candidiasis reported 8 or more years and 66 (12%) reported 5 or more years of, disease 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.36 The new antidiabetic agents SGLT2 inhibitors (dapagliflozin and canagliflozin), which increase glycosuria, also increase episodes of vulvovaginal candidiasis.16,37,38 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.19,39,40 Antibiotic use increases the rate of vulvovaginal candidiasis—by 23% in one questionnaire study of vulvovaginitis,24 which is caused by *Candida* spp in more than 90% of cases.41 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.15,42 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.15 Most women with vulvovaginal candidiasis who were taking HRT had a history of the infection (23 of 43 [67%]) 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.43 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.44 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.26 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.20 A survey of bacterial vaginosis in teenagers in Ecuador found a remarkably high prevalence compared with that in Europe,45 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,46,47 which means our figure is likely to be an underestimate of overall loss due to time off work for recurrent vulvovaginal candidiasis. Finally, our estimates are based entirely on data from 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,10,48 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.49,50 Vaccine efficacy was partial, particularly in those younger than 40 years of age. Should this vaccine prove its worth clinically, this would provide a major benefit to affected women.

Despite these 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; diabetic women, those requiring frequent antibiotics usually for relapsing chest or urinary infections, cystic fibrosis sufferers, 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. Some women get bacterial vaginosis and vulvovaginal candidiasis, and a rapid, point of care test to distinguish them would be of enormous value in treatment decision-making. Azole resistance is probably addressable with such an approach, with potential for minimizing the impact of oral triazole resistance allowing successful suppressive therapy. For those with resistance, alternative antifungal therapies are on the horizon. Improvement of women’s health is realistic target by addressing the frequent problem of recurrent vulvovaginal candidiasis

**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, and in Novacyt, which markets the Myconostica real-time molecular assays. He acts or has recently acted as a consultant to Astellas, Sigma-Tau, Basilea, Scynexis, Cidara, Biosergen, Quintiles, Pulmatrix, Pulmocide, and Zambon. In the past 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck, and Pfizer All other authors declare no competing interests.

**References**

1 Sobel JD. Vulvovaginal candidosis. *Lancet* 2007; **369:** 1961–71.

2 Gonclaves B, Ferreira C, Alves CT, et al. Vulvovaginal candidiasis: epidemiology, microbiology and risk factors. *Crit Rev Microbiol* 2015; **42:** 905–27.

3 Ilkit M, Guzel AB. The epidemiology, pathogenesis, and diagnosis of vulvovaginal candidosis: a mycological perspective. *Crit Rev Microbiol* 2011; **37:** 250–61.

4 Fischer G. Chronic vulvovaginal candidiasis: what we know and what we have yet to learn. *Australas J Dermatol* 2012; **53:** 247–54.

5 Hong E, Dixit S, Fidel PL, Bradford J, Fischer G. Vulvovaginal candidiasis as a chronic disease: diagnostic criteria and definition. *J Low Genit Tract Dis* 2014; **18:** 31–38.

6 Aballéa S, Guelfucci F, Wagner J, et al. Subjective health status and health-related quality of life among women with recurrent vulvovaginal candidosis (RVVC) in Europe and the USA. *Health Qual Life Outcomes* 2013; **11:** 169.

7 Chapple A. Vaginal thrush: perceptions and experiences of women of south Asian descent. *Health Educ Res* 2001; **16:** 9–19.

8 Irving G, Miller D, Robinson A, Reynolds S, Copas AJ. Psychological factors associated with recurrent vaginal candidiasis: a preliminary study. *Sex Transm Infect* 1998; **74:** 334–38.

9 Powell K. Vaginal thrush: quality of life and treatments. *Br J Nurs* 2010; **19:** 1106–11.

10 Sobel JD. Recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol* 2016; **214:** 15–21.

11 Corsello S, Spinillo A, Osnengo G, et al. An epidemiological survey of vulvovaginal candidiasis in Italy. *Eur J Obstet Gynecol Reprod Biol* 2003; **110:** 66–72.

12 Sobel JD. Recurrent vulvovaginal candidiasis. Am J Obstet Gynecol. 2016

Jan;214(1):15-21.

13 Bayer. 2013 integrated annual report. https://www.bayer.com/en/ar-2013.pdfx?forced=true (accessed Feb 12, 2018).

14 Pfizer. Financial report 2013. http://www.annualreports.co.uk/HostedData/AnnualReportArchive/p/NYSE\_PFE\_2013.pdf (accessed Feb 12, 2018).

15 Fischer G, Bradford J. Vulvovaginal candidiasis in postmenopausal women: the role of hormone replacement therapy. *J Low Genit Tract Dis* 2011; **15:** 263–67.

16 Nyirjesy P, Sobel JD, Fung A, et al. Genital mycotic infections with canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. *Curr Med Res Opin* 2014; **30:** 1109–19.

17 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339:** b2535.

18 Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is “quality of evidence” and why is it important to clinicians? *BMJ* 2008; **336:** 995–98.

19 UN. World population prospects: the 2012 revision, DVD edition. New York, NY: United Nations, 2013.

20 Foxman B, Muraglia R, Dietz J-P, Sobel JD, Wagner J. Prevalence of recurrent vulvovaginal candidiasis in 5 European countries and the United States: results from an internet panel survey. *J Low Genit Tract Dis* 2013; **17:** 340–45.

21 Ferris DG, Nyirjesy P, Sobel JD, Soper D, Pavletic A, Litaker MS. Over-the-counter antifungal drug misuse associated with patient-diagnosed vulvovaginal candidiasis. *Obstet Gynecol* 2002; **99:** 419–25.

22 Ryan-Wenger NA, Neal JL, Jones AS, Lowe NK. Accuracy of vaginal symptom self-diagnosis algorithms for deployed military women. *Nurs Res* 2010; **59:** 2–10.

23 Sihvo S, Ahonen R, Mikander H, Hemminki E. Self-medication with vaginal antifungal drugs: physicians' experiences and women's utilization patterns. *Fam Pract* 2000; **17:** 145–49.

24 Vergers-Spooren H, van der Meijden W, Luijendijk A, Donders G. Self-sampling in the diagnosis of recurrent vulvovaginal candidosis. *J Low Genit Tract Dis* 2013; **17:** 187–92.

25 Beigi R, Meyn L, Moore D, Krohn M, Hillier S. Vaginal yeast colonization in nonpregnant women: a longitudinal study. *Obstet Gynecol* 2004; **104:** 926–30.

26 Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Candida vaginitis: self-reported incidence and associated costs. *Sex Transm Dis* 2000; **27:** 230–35.

27 Güzel AB, Küçükgöz-Güleç U, Aydin M, Gümral R, Kalkanci A, Ilkit M. Candida vaginitis during contraceptive use: the influence of methods, antifungal susceptibility and virulence patterns. *J Obstet Gynaecol* 2013; **33:** 850–56.

28 Johnson SR, Griffiths H, Humberstone FJ. Attitudes and experience of women to common vaginal infections. *J Low Genit Tract Dis* 2010; **14:** 287–94.

29 Pirotta MV, Gunn JM, Chondros P. "Not thrush again!" Women's experience of post-antibiotic vulvovaginitis. *Med J Aust* 2003; **179:** 43–46.

30 Sawyer SM, Bowes G, Phelan PD. Vulvovaginal candidiasis in young women with cystic fibrosis. *BMJ* 1994; **308:** 1609.

31 Bang RA, Bang AT, Baitule M, Choudhary Y, Sarmukaddam S, Tale O. High prevalence of gynaecological diseases in rural Indian women. *Lancet* 1989; **1:** 85–88.

32 Otero L, Palacio V, Carreño F, Méndez FJ, Vázquez F. Vulvovaginal candidiasis in female sex workers. *Int J STD AIDS* 1998; **9:** 526–30.

33 Rylander E, Berglund AL, Krassny C, Petrini B. Vulvovaginal candida in a young sexually active population: prevalence and association with oro-genital sex and frequent pain at intercourse. *Sex Transm Infect* 2004; **80:** 54–57.

34 Organisation for Economic Co-operation and Development. OECD.Stat. Paris, France: Organisation for Economic Co-operation and Development, 2014.

35 Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380:** 2163–96.

36 Emanuel EJ. Sex and the single senior. *The New York Times* (New York), Jan 18, 2014.

37 Johnsson KM, Ptaszynska A, Schmitz B, Sugg J, Parikh SJ, List JF. Vulvovaginitis and balanitis in patients with diabetes treated with dapagliflozin. *J Diabetes Complications* 2013; **27:** 479–84.

38 Nyirjesy P, Zhao Y, Ways K, Usiskin K. Evaluation of vulvovaginal symptoms and Candida colonization in women with type 2 diabetes mellitus treated with canagliflozin, a sodium glucose co-transporter 2 inhibitor. *Curr Med Res Opin* 2012; **28:** 1173–78.

39 Lyon A, Gunn E, Haworth D, Bilton D. Is genital Candida infection a significant problem for adults with cystic fibrosis? *J Cystic Fibrosis* 2004; **3** (suppl 1)**:** 97 (abstract 373).

40 Woolnough EM SC DM, Jones A, Webb AK. Is candidiasis a problem in adults with cystic fibrosis? A prospective study. *Thorax* 2004; **59:** S78.

41 Bluestein D, Rutledge C, Lumsden L. Predicting the occurrence of antibiotic-induced candidal vaginitis (AICV). *Fam Pract Res J* 1991; **11:** 319–26.

42 Dennerstein GJ, Ellis DH. Oestrogen, glycogen and vaginal candidiasis. *Aust N Z J Obstet Gynaecol* 2001; **41:** 326–28.

43 Jolleys JV, Olesen F. A comparative study of prescribing of hormone replacement therapy in USA and Europe. *Maturitas* 1996; **23:** 47–53.

44 Kent HL. Epidemiology of vaginitis. *Am J Obstet Gynecol* 1991; **165:** 1168–76.

45 Vaca M, Guadalupe I, Erazo S, et al. High prevalence of bacterial vaginosis in adolescent girls in a tropical area of Ecuador. *BJOG* 2010; **117:** 225–28.

46 Mitchell RJ, Bates P. Measuring health-related productivity loss. *Popul Health Manag* 2011; **14:** 93–98.

47 Nicholson S, Pauly MV, Polsky D, Sharda C, Szrek H, Berger ML. Measuring the effects of work loss on productivity with team production. *Health Econ* 2006; **15:** 111–23.

48 Donders G, Bellen G., Byttebier G, et al. Individualized decreasing-dose maintenance fluconazole regimen for recurrent vulvovaginal candidiasis (ReCiDiF trial). *Am J Obstet Gynecol* 2008; **199:** 613.e1–9.

49 De Bernardis F, Amacker M, Arancia S, et al. A virosomal vaccine against candidal vaginitis: immunogenicity, efficacy and safety profile in animal models. *Vaccine* 2012; **30:** 4490–98.

50 Schmidt CS, White CJ, Ibrahim AS, et al. NDV-3, a recombinant alum-adjuvanted vaccine for Candida and Staphylococcus aureus, is safe and immunogenic in healthy adults. *Vaccine* 2012; **30:** 7594–600.

**Figure 1: Patterns of vulvovaginal candidiasis**

(A) Uncomplicated vulvovaginal candidiasis during reproductive life (approximate 75% lifetime risk). (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).

**Figure 2: Literature search and study selection**

Searches conducted and the final disposition of all articles identified, including those found in our files and in combing the references of the articles identified. The reasons for exclusion were usually multiple, but the commonest was a lack of a suitable denominator to assess point prevalence. Two articles were excluded because the translation from a foreign language made it clear that they did not fulfill the diagnostic criteria for rVVC and/or have an appropriate denominator

**Figure 3: Estimated age-specific global prevalence of recurrent vulvovaginal candidiasis**

Base case is 75% of the estimate reported by Foxman and colleagues,20 with lower (–33%) and upper (+33%) sensitivity analyses

**Figure 4: Global prevalence of recurrent vulvovaginal candidiasis per 100 000 women**

Estimated using the 6% flat rate for 15-54 years of age.. Prevalence primarily reflects the variable demographics of women in their reproductive years globally.

**Search strategy and selection criteria**

These are described in detail in the Methods section.