

OVERVIEW BRIEF

**PPD**<sup>®</sup>



February 2018

## Vulvovaginal Candidiasis (VVC) and Recurrent VVC (RVVC)

Regulatory requirements vs. standard of care in  
clinical development.

Between 50 and 75% of all women develop vulvovaginal candidiasis (VVC) at least once in their lives. Recurrent VVC (RVVC) is defined as four or more episodes of confirmed VVC within 12 months, with an estimated prevalence of 5-6%. PPD investigated key differences between standard medical practice and recent regulatory guidance for VVC products development. These key differences present operational challenges for VVC and RVVC clinical trials.

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## Acute, recurrent and chronic VVC

Uncomplicated vulvovaginal candidiasis (VVC) is generally defined as a single episode of vaginal inflammation caused by *Candida* yeast in an otherwise healthy female<sup>1</sup>, and is characterized by vaginal discharge, vulvovaginal edema and erythema, pruritus, burning sensation and pain, as the most common symptoms.

If four or more episodes of VVC occur in a patient within 12 months, it is defined as **recurrent VVC** (RVVC), which is classified as a type of “complicated” VVC. Another form of VVC is **chronic VVC** (CVVC)<sup>2</sup>, where female subjects remain highly symptomatic despite low microscopy count, and may support the notion of a hypersensitivity reaction, which continues in the absence of detectable *Candida* in the vagina.

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## Prevalence and economic burden

Each year, an estimated 10 million health care office visits to gynecologists are due to vulvo-vaginitis. One survey reports that 73% of women with vaginitis symptoms including itching, vaginal discharge and vulvar irritation (presumed to be due to VVC/RVVC, but, not confirmed to be caused by *Candida*) have resorted to over-the-counter (OTC) medications to reduce health care costs and avoid expensive office visits<sup>3</sup>. The burden of cost of VVC to the community is significant and has been estimated at \$1.8 billion per year in the United States. Topical, intravaginal antifungal medications (imidazoles) have been available OTC since the early to mid-1990s in the U.S. and EU, respectively<sup>4</sup>. Additionally, an overabundance of vaginal anti-itch creams and homeopathic treatments are widely available in grocery stores, supermarkets, pharmacies and health food stores<sup>3</sup>.

Vaginal colonization with *Candida*, a prerequisite for development of VVC, occurs in at least 40% of adult women at any given point. RVVC prevalence is estimated to be 5-6%, however underreporting should be considered since patients frequently self-diagnose and self-treat with widely available OTC antifungal and homeopathic preparations.

It has been calculated that RVVC results in a mean of 33 lost work hours/year, costing €266-1,130 per woman per year in Europe, and \$1,261 per woman per year in the U.S.<sup>5</sup>.

## Regulatory requirements

According to the U.S. Food & Drug Administration (FDA) Draft Guidance (July 2016) for Industry “Vulvovaginal Candidiasis: Developing Drugs for Treatment,” there are specific efficacy trial considerations that should be considered in developing drugs for VVC treatment purposes.

## Clinical microbiology considerations

- Vaginal swabs should be obtained for microbiological evaluations
- Specimens collected to aid in the diagnosis should be examined microscopically for the presence of yeasts, e.g., a wet mount prepared in a potassium hydroxide solution (**KOH**)
- Specimens should be **cultured** using standard fungal media

## Enrollment criteria

Enrollment criteria included clinical diagnosis of VVC, defined as having a white or creamy vaginal discharge, plus the following:

## Signs and symptoms of VVC

**Two or more** of the following signs and symptoms of VVC that are characterized as **moderate or severe**: itching, burning, irritation, edema, redness or excoriation.

## KOH or saline preparation

Revealing yeast forms (hyphae or pseudo-hyphae) or budding yeast.

## Normal vaginal pH

Greater than or equal to 4.5.

## Diagnostic practices survey

In 2016, PPD conducted a survey to investigate country-level diagnostic practices relating to acute and recurrent VVC, interviewing 28 investigators in 13 countries worldwide. The most striking evidence found was the great variation in the use of diagnostics to confirm VVC and RVVC. In many cases diagnostics were not utilized for every episode of VVC/RVVC that occurred. Also, with respect to diagnostic tests used routinely, we found that many sites do perform microscopy on saline wet preparations, but they do not always perform microscopy on a KOH prep. Instead, many sites use the KOH prep to conduct a "whiff test."

Because of the unexpected findings from the 2016 survey, an additional survey was planned to discern the main differences between standard practice and clinical trials in VVC/RVVC. In October 2017, we developed and conducted a new survey (Table 1) for this purpose. For this survey, we focused on countries in Eastern Europe, where reported RVVC prevalence is quite high (> 4000 cases/100.000).

Our new survey involved 58 sites in Bulgaria, Hungary, Poland and Russia.

Table 1 – PPD VVC/RVVC Survey Response

Countries Involved	Investigational Sites Involved	Response Rate
4	58	81%

## Survey objective

The objective of our survey was to investigate:

- Common (standard) medical practice to diagnose VVC and RVVC
- Tendency of patients to self-treat with use of OTC drugs for VVC
- Discrepancies between standard medical practice and regulatory requirements in a clinical trial setting

The survey included six questions, listed in Table 2 below.

Table 2 – Survey Questions

Survey Questions	
1	How many female subjects (ages 12 or older) with RVVC (defined as three or more VVC episodes in the last 12 months) confirmed by medical history do you see at your site?
2	What percentage of these subjects has documentation of at least one previous VVC episode in the last 12 months by a positive culture, PCR, Affirm test, KOH test or a documented Papanicolaou (Pap) test in the prior 12 months revealing filamentous hyphae/pseudo-hyphae and/or budding yeast cells?
3	What percentage of these subjects will have documentation of a Pap test in their medical record (depending on appropriate screening age per local guidelines)?
4	In your practice setting, how common is it for women with symptoms of VVC to treat with OTC medications without any medical consultation (office visit or phone call to health care provider)?
5	When a woman presents with symptoms suggestive of acute VVC, how is she evaluated? (For each--select always, sometimes, rarely or never): a) Exam; b) Saline wet prep microscopy; c) KOH microscopy; d) PCR for yeast; e) Yeast culture; f) Other – please specify.
6	When a woman presents with symptoms suggestive of RVVC, how is she evaluated? (For each--select always, sometimes, rarely or never): a) Exam; b) Saline wet prep microscopy; c) KOH microscopy; d) PCR for yeast; e) Yeast culture; f) Other – please specify.

## Survey method

A total of 58 investigational sites were selected from PPD global site selection database in Bulgaria, Hungary, Poland and Russia, based on their previous experience in VVC (Table 3).

Table 3 – PPD VVC/RVVC Survey Method

Countries	Sites Contacted	Questionnaires received (%)
BULGARIA	22	22 (100%)
HUNGARY	9	8 (89%)
POLAND	12	7 (58%)
RUSSIA	15	10 (66%)
TOTAL	58	47 (81%)

Investigational sites were contacted to assess their interest in participating to the survey. In case of interest, an invitation was sent by e-mail to complete the survey remotely within 4 weeks. All sites were contacted up until the end of the 4-week given period, with at least weekly reminders. At end of the given period, all further contact was stopped with sites that didn't return a survey.

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58 investigational sites selected to complete the survey, based on their previous experience in VVC

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## Survey outcome

### Number of cases with documented RVVC in medical records

The goal of the survey was to primarily understand the number of RVVC cases confirmed and documented in the medical history of patients treated at sites.

RVVC was defined as three or more episodes in the last 12 months, in women ages 12 and older and the median value of women diagnosed with RVVC per site (documented in medical history) was **60** cases.

### Documented episodes in the last 12 months confirmed with diagnostic tests

The survey initially established the number of cases per site as the baseline value, and requested the following information:

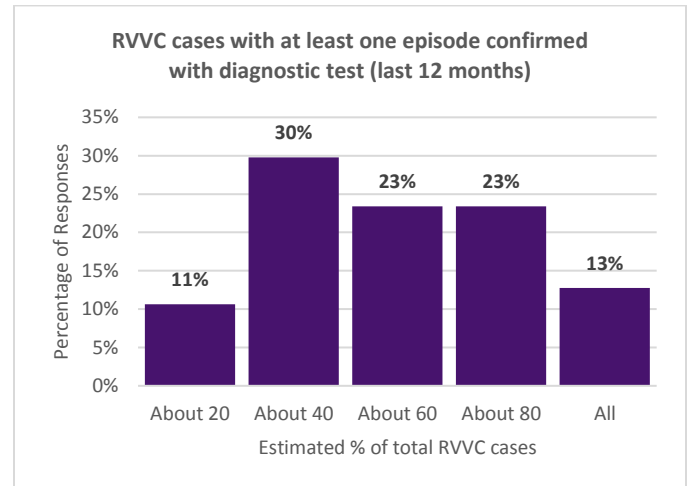
- How recurrent episodes are documented in RVVC, e.g., if a diagnostic test among those commonly used to confirm VVC is regularly performed as standard practice
- Percentage of cases with at least one episode of VVC in the last 12 months confirmed with a diagnostic test, e.g., KOH, PCR, Affirm or Pap

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About **50% of total RVVC cases** have at least one episode in the last 12 months confirmed with a diagnostic test

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Figure 1 – RVVC cases with at least one episode confirmed with diagnostic test (last 12 months)



In approximately 90% of responses, at least 40% of RVVC patients have a documented episode in the last 12 months, confirmed with a diagnostic test. **This is a key element to consider for its expected impact on trial eligibility of the RVVC population**, if a historical confirmation of diagnosis is required in addition to the screening procedures.

The clinical validity of older diagnostic confirmation (greater than one to two years) would not be an acceptable proxy for new vaginitis complaints or symptoms. Recurrences (RVVC), therefore, cannot be documented based on patient-reported or medical record prescriptions of vaginal or oral antifungal medications for the treatment of repeated acute episodes. While there is variation in practice patterns, self-medication with OTC imidazoles is only recommended for:

- Recurrence of previously diagnosed (by healthcare professionals) VVC
- Persistent symptoms after OTC treatment with imidazole/antifungals
- Recurrent symptoms within two months of treatment

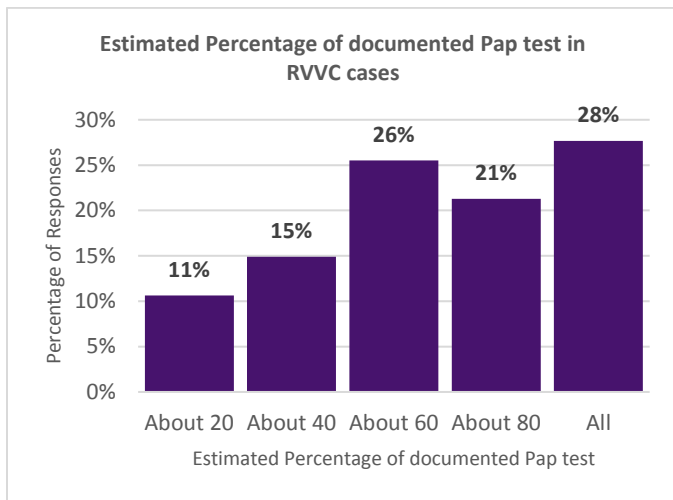
Inappropriate self-treatment and lack of documentation of office work-up of vaginitis (cultures, KOH, vaginal pH) present a significant challenge for meeting the diagnosis criteria for RVVC clinical trials, despite the known prevalence rate of VVC and RVVC.

### Documented Pap Test

In this gynecological diagnostic framework, the availability of a documented Pap test is also an important screening, e.g., inclusion factor, to exclude any ongoing or pre-cancerous cervical dysplasia or atypia.

In addition, the VVC diagnostic confirmation procedures also assessed the percentage of women among the RVVC population with a Pap test documented in medical records.

Figure 2 – Estimated percentage of RVVC cases with documented Pap test in medical records



In approximately 90% of responses, it was estimated that at least 40% of the RVVC population cases have a documented Pap test available. However, the survey question specified “depending on appropriate screening age per local guidelines.” We can therefore reasonably assume that for the remaining percentage, a Pap test is not yet performed per local screening requirements (age and/or condition).

## Use of OTC antifungal products with and without medical advice

It is difficult to know accurately the true incidence of RVVC<sup>2</sup>, because of the widespread self-diagnosis and self-treatment used with OTC medications.

As a common condition, VVC is also regarded to be a minor medical complaint that is suitable for self-medication<sup>4</sup>. However, there are specific parameters for self-treatment according to the labelling of OTC vaginal antifungal drugs and specific considerations regarding the limitations and challenges of self-treatment:

- Under the surveillance of a physician in the case of a first infection, if it is the third infection during the past six months, if the woman is under 16 years old or if it is during the first trimester of pregnancy<sup>4</sup>
- Despite the introduction of OTC drugs for treatment of vulvo-vaginitis, the costs of health care office visits to treat this disorder rose to an estimated of \$3.1 billion by 2014<sup>3</sup>
- Women have proven to be inadequate in self-diagnosis, and women with a previous clinical

diagnosis of *Candida* infection were not more accurate at identifying their current condition<sup>3</sup>

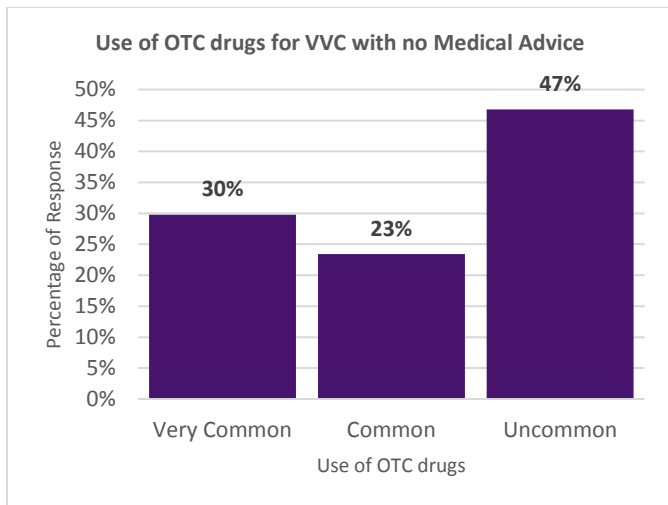
- Studies on women treating themselves for candidiasis revealed a 28% accuracy rate<sup>6</sup>
- The most common cause of infectious vulvo-vaginitis is bacterial vaginosis, which can also present with symptoms of vaginal discharge with itching. Bacterial vaginosis has been found to be twice as prevalent as yeast vaginitis<sup>4</sup>
- Many patients who self-treat for presumed VVC are likely erroneously self-treating bacterial vaginosis with an antifungal product that is not effective against bacterial vaginosis

While the tendency to self-treat is often due to the acute discomfort caused by vaginitis which necessitates prompt treatment, self-treating also allows women to minimize out-of-pocket costs and avoid an expensive and time-consuming visit to their health care provider<sup>3</sup>.

Self-treatment additionally underscores **the lack of patients’ awareness** of the importance of episode frequency for a different diagnosis and implications for a substantial change in the treatment approach from topical and short term to systemic and long term. It should be noted that women with chronic or persistent *Candida* infections are less likely to respond to short courses of therapy and should consult with a physician or other qualified health care provider about a specific treatment regimen. They are, therefore, not candidates for OTC therapy.

The FDA 2016 guidance requires exclusion from VVC trials of patients “who were treated for VVC within the past month.” Both in VVC and RVCC trials, information around the tendency to self-treat becomes important for eligibility screening around medications used to treat episodes of VVC without medical advice

Figure 3 – Estimated behavioral approach of patients to self-treat in VVC episodes.



Based on responses to the self-treatment question, for approximately half of the patients it is uncommon to use OTC drugs without any medical advice. However, for the remaining half of the population it is common or even very common to use OTC drugs.

No major differences were found regarding responses provided by country, showing inter-site rather than intercountry differences, except for Hungary, where all sites reported as very uncommon for patients to use OTC drugs for VVC with no medical advice.

No major differences found in patients' tendency to use OTC drugs for VVC, except for Hungary

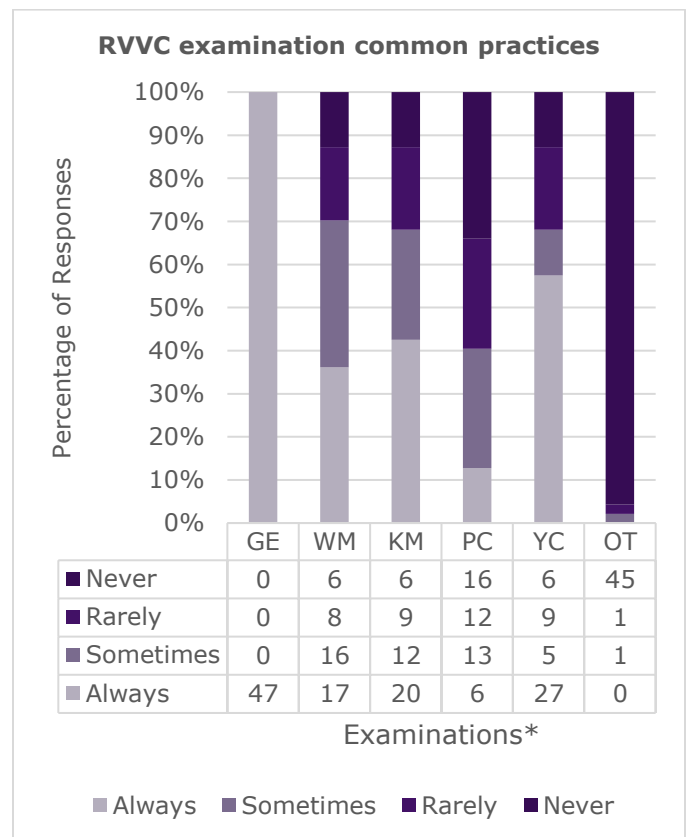
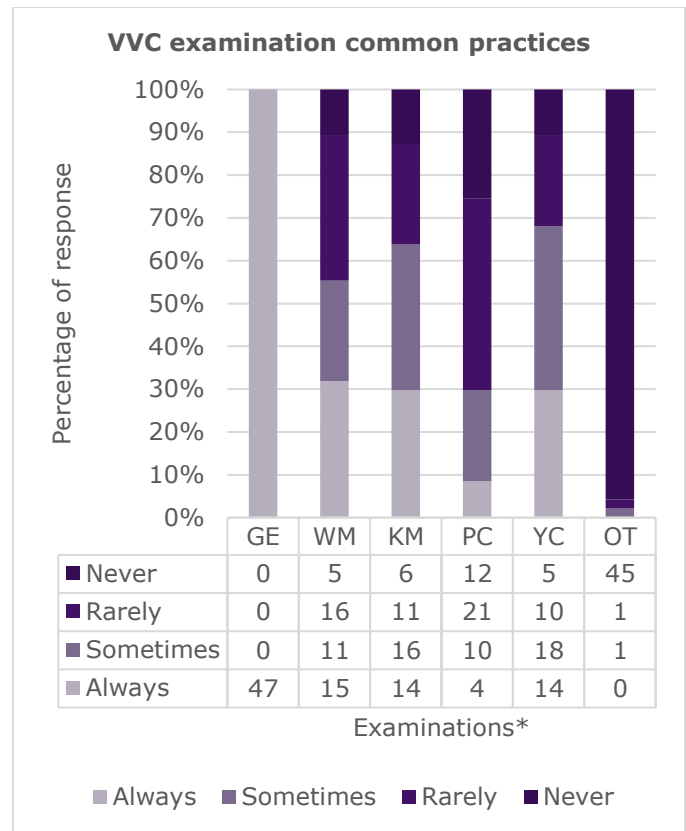
### VVC vs. RVVC assessment – A standard practice comparison

We previously described the regulatory requirements (FDA draft guidance) for clinical microbiology considerations, including KOH testing and culture for the presence of yeast.

The survey assessed if and how much local diagnostic practices for the assessment of VVC and RVVC differ from regulatory requirements and gaps to be covered prospectively in preparation of conducting clinical trials.

The survey assessed how VVC and RVVC diagnoses are performed and confirmed, specifying the most common procedure among gynecological examination, saline wet mount, KOH microscopy, PCR for yeast identification, yeasts culture or other – to be specified.

Figure 4 – Preference in examinations for VVC and RVVC diagnostic assessment



\* GE = Gynecological examination, WM = Wet mount, KM = KOH microscopy, PC = PCR, YC = Yeasts culture, OT = Others.

By a comparison of examinations for acute VVC assessment it appears that gynecological examination is always performed. This is followed by wet mount and/or KOH microscopy in about 50% of cases (always, sometimes), while PCR and yeast culture are less common.

For the assessment of RVVC, gynecological examination is also always performed, followed by wet mount and KOH microscopy, but with an increase of preference toward the collection of yeast culture. This 100% increase (14 to 28) in yeast culture preference from VVC to RVVC diagnosis is the most striking difference, which is understandable based on the necessity to identify *C. glabrata* and other *non-albicans Candida* species, because conventional anti-mycotic therapies are not as effective against these nonalbicans species as against *C. Albicans*<sup>7</sup>. A few "other" alternative methods were reported in both cases, which are methylene-blue microscopy and pH check.

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## 100% increase of yeast culture preference, in diagnosing from VVC to RVVC

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Pharmaceutical companies with plans for the clinical development of drugs for the treatment of VVC and RVVC should consider, according to the responses we obtained that:

- Gynecological examination is always performed to assess diagnostic procedures for VVC and RVVC
- Wet mount and/or KOH microscopy are not always (regularly) performed along with gynecological examination; instead, standardization of clinical practices for diagnosis confirmation is recommended
- Also, *Candida* culture are not regularly performed. However, preference to this diagnostic confirmation is increased in case of suspected RVVC, probably to decide for a change in the therapeutic (treatment) approach to the infection

## Discussion

VVC is a common problem associated with a high level of morbidity.

Many women self-medicate vaginitis symptoms with OTC anti-fungal or homeopathic treatments, often inappropriately with off-label use, potentially obscure the correct diagnosis and receive false-negatives when medication has been used before microbiologic

confirmation. Therefore, it is difficult to assess the prevalence of RVVC.

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## It is difficult to calculate accurately the prevalence of RVVC due to tendency of patients to self-diagnosis and self-treat

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Globally, there is a higher prevalence of VVC in pregnant women, women with poorly controlled diabetes and women who are immunocompromised<sup>8</sup>. There also has been increased focus by global regulatory authorities on women's health/reproductive health product development including Guidance for Industry for VVC (2016), Bacterial Vaginosis (2016) HPV IN Vitro Diagnostic Devices (2017), Pregnancy and Lactation Labeling Final Rule (2014) in the U.S. and Urinary Incontinence (2014) in Europe.

Study protocol requirements such as inclusion and exclusion criteria or treatment scheme can be different, at a variable degree, from the standard practices for the diagnosis and treatment of diseases.

The focus of the surveys was to investigate these differences in VVC and RVCC for an earlier identification of gaps to be covered in clinical trial settings. The 2017 survey focused on Eastern Europe because of the overall higher VVC disease prevalence.

## Summary of survey findings

Based on their experience in VVC, 58 investigational sites were pre-selected from our global site selection database in Bulgaria, Hungary, Poland and Russia, and were proposed to participate in our survey. If interested, sites submitted a short six-item questionnaire and given four weeks to complete. Eventually, 47 completed questionnaires were returned with an overall response rate of 81%.

Generally, the following trends were found in VVC and RVVC standard diagnostic practice:

- Approximately 50% of total patients with documented diagnosis of RVVC have had at least one episode in the past 12 months confirmed with a diagnostic test
- Diagnostic approach from VVC to RVVC is similar, except for a doubling in the preference of yeasts culture if RVVC is suspected
- Patients' tendency to self-medicate VVC/RVVC, which is already known to be an issue, is confirmed in 50% of cases

The FDA draft guidance "Vulvovaginal Candidiasis: Developing Drugs for Treatment" in the clinical

microbiology considerations requires vaginal swab specimen to be tested for the presence of yeast (wet mount prepared with KOH) and cultured for identification.

## Conclusions

While gynecological examination is performed in all cases of suspected VVC/RVVC infection, other diagnostic tests are executed in approximately 50% of cases, with variability between the standard practice at investigational sites. Preference for yeast culture is doubled for suspected RVVC.

Therefore, pharmaceutical sponsors with an interest in clinical development for VVC/RVVC products should carefully consider the tendency to achieve an overall standardization of practices among the investigational sites involved in a trial.

Patients' tendency for self-diagnosis and self-treatment is a known limiting factor for an accurate estimation of RVVC prevalence, which is confirmed in the responses provided from sites.

While patients generally should be counseled for medical care vs. self-diagnosis and treatment, in a clinical trial setting this becomes even more important to ensure that eligible patients are successfully directed to enrollment. This can be achieved by establishing a successful network with health care providers in the relevant area (family doctors, gynecologists, pharmacies, etc.) to pre-identify eligible patients for enrollment.

## References

1. FDA Guidance: Vulvovaginal Candidiasis: Developing Drugs for Treatment Guidance for Industry. Draft Guidance, July 2016.
2. Vulvovaginal Candidiasis as a Chronic Disease: Diagnostic Criteria and Definition. 2013, American Society for Colposcopy and Cervical Pathology, *Journal of Lower Genital Tract Disease*, Volume 18, Number 1, 2014, 31Y38.
3. Vaginitis: Making Sense of Over-the-Counter Treatment Options Lauren B. Angotti, Lara C. Lambert, and David E. Soper. *Infect Dis Obstet Gynecol*. 2007; 2007: 97424.
4. Self-medication with vaginal antifungal drugs: physicians' experiences and women's utilization patterns, Sinikka Sihvo Riitta Ahonen Heli Mikander Elna Hemminki, *Family Practice*, Volume 17, Issue 2, 1 April 2000, Pages 145-149, <https://doi.org/10.1093/fampra/17.2.145>.
5. Aballéa et al. Health and Quality of Life Outcomes 2013, 11:169, <http://www.hqlo.com/content/11/1/169>

6. Vaginitis. Katz. *Comprehensive Gynecology*. 5<sup>th</sup> ed. Mosby; Elsevier; 2007. 588-596.
7. CDC: <https://www.cdc.gov/std/tg2015/candidiasis.htm>
8. Vaginal thrush: quality of life and treatments. Karen Powell, *British Journal of Nursing*, 2010, Vol 19, No 17.

## Limitations

Outcome and conclusions generated in this research are limited to the sample size, the number of responses collected and the geographical distribution of the investigational sites.

Criteria for participation in the survey for sites included interest and ability to participate in a VVC clinical trial (skill with KOH, microscopy to detect yeast at the point of care, equipment, and experience in office microscopy and specimen collection). This requirement may have skewed the responses. Many sites declined to participate because they do not perform office microscopy as part of their diagnostic work-up for vaginitis. The 2016 U.S. site survey encountered many sites that did not routinely perform office microscopy due to CLIA regulations, and did not have recent experience in these procedures.

In the future, it is our aim to extend this survey in the U.S., checking if the trends identified in Europe are confirmed, or new differences will be found.

Outcome and results of the survey might be different with the inclusion of new countries, currently not involved in our research.