Unsatisfactory rates vary between cervical cytology samples prepared using ThinPrep and SurePath platforms: a review and meta-analysis

Daniel Fontaine,1 Nadira Narine,2 Christopher Naugler1

ABSTRACT

Objective: To compare unsatisfactory rates between the two major liquid-based cytology (LBC) platforms, namely ThinPrep (Hologic) and SurePath (Becton Dickinson).

Design: The authors performed both a systematic review and a meta-analysis. Inclusion criteria were English language, data presented on unsatisfactory rates for either ThinPrep or SurePath, utilising actual patient samples (ie, not laboratory manipulated samples) and no manipulation using acetic acid to increase the satisfactory rate. The authors searched PubMed for articles using the keywords ‘SurePath’ or ‘ThinPrep’ and ‘unsatisfactory’. References of retrieved studies were searched for additional articles. Key researchers in the field were also contacted.

Participants and interventions: Eligible studies were reviewed for rates of unsatisfactory cervical cytology smears processed on either the ThinPrep or SurePath platforms (compared with a general linear model) or data on unsatisfactory rates for both platforms for the same laboratory and the same patient population (compared with a meta-analysis using a random effects model and pooled RR).

Primary Outcome Measure: Unsatisfactory rate of cervical cytology smears.

Results: A total of 1 120 418 cervical cytology smears were reported in 14 different studies using the SurePath platform for an overall unsatisfactory rate (weighted average) of 0.3%. 28 studies reported on 1 148 755 smears prepared using the ThinPrep platform for an overall unsatisfactory rate (weighted average) of 1.3%. The general linear model did not show a difference between LBC platforms when other variables were controlled for; however, the power to detect a difference (0.087) was very low. The meta-analysis performed on four studies where both ThinPrep and SurePath results were reported from the same laboratory showed fewer unsatisfactory tests from the SurePath platform (RR 0.44, 95% CI 0.25 to 0.77, p=0.004).

Conclusions: Multiple factors affect LBC unsatisfactory rates. In a meta-analysis, cervical cytology samples prepared on the SurePath platform show significantly fewer unsatisfactory smears than those prepared on the ThinPrep platform.

ARTICLE SUMMARY

Article focus
- Two major LBC platforms are commonly used (ThinPrep (Hologic) and SurePath (Becton Dickinson))
- These employ different sample preparation methodologies, which may result in different unsatisfactory rates.

Key messages
- Multiple factors are associated with LBC unsatisfactory rates.
- Cervical cytology samples prepared on the SurePath platform show significantly fewer unsatisfactory smears than those prepared on the ThinPrep platform.
- Unsatisfactory samples represent a missed opportunity for screening

Strengths and limitations of this study
- Large sample size from multiple studies
- Relatively few studies performed a head-to-head evaluation of the two platforms
- Restriction to English literature and use of only one bibliographic search base (Medline) are limitations.

INTRODUCTION

Since first introduced in the late 1990s, liquid-based cytology (LBC) was quickly adopted by many laboratories as a great improvement in the performance of gynaecologic cytology. The method permits laboratories to create slides rather than having prepared slides sent to them in various degrees of fixation and preparation. The LBC methodology also provides a cleaner smear as the proprietary methods remove obscuring elements such as blood and inflammation. This ‘cleaning’ of samples is often cited as the reason there are lower unsatisfactory rates in LBC.1 The liquid
platforms also allow for reflex testing for human papilloma virus for borderline cases. However, large trials and a meta-analysis have recently shown that the performance of LBC may be equivalent to conventional cytology, thus making it difficult for laboratories to justify the added expense of LBC.2–4

When considering LBC, laboratories are faced with a decision between two main platforms produced by ThinPrep (Hologic) and SurePath (Becton Dickinson). Both technologies are Food and Drug Administration approved but employ different methodologies in sample preparation. In light of these differences in preparation, we set out to evaluate the existing English literature comparing the performance of each platform with respect to unsatisfactory rates.

METHODS
Information sources and search strategy
Our meta-analysis adhered to the PRISMA statement for reporting on meta-analyses.5 The initial literature search for articles was conducted using PubMed. Articles published in English between 1 January 1990 and 1 August 2011 were retrieved using the search words ‘unsatisfactory’ and ‘ThinPrep or SurePath’. These date range were chosen to coincide with the period following the introduction of The Bethesda System (TBS) in 1989.6 The references of the retrieved papers were examined for further possible studies not detected in the initial literature search. Additionally, we searched major clinical trial registries (http://clinicaltrials.gov, http://isrctn.org, http://www.umin.ac.jp/ctr/index.htm/, http://www.anzctr.org.au/Default.aspx, http://www.trialregister.nl/trialreg/index.asp, http://apps.who.int/trialsearch) using the search words ‘liquid-based cytology’, contacted both manufacturers and contacted key researchers in the field to check for ongoing or unpublished studies.

Study selection and eligibility criteria
Eligible studies for the review presented rates of technically unsatisfactory cervical cytology smears performed on either ThinPrep or SurePath platform. For inclusion in the meta-analysis, studies must have presented data on unsatisfactory cervical cytology smears performed on both ThinPrep and SurePath platforms by the same laboratory on the same patient population. Only studies presented in English were considered. Both published and unpublished studies were considered to be eligible for inclusion.

The initial search retrieved 76 papers. The abstracts of these papers were reviewed by CN and DF and 46 were chosen for full review. An additional six published studies were subsequently identified as well as one unpublished study. Of these articles, 42 met the further inclusion criteria of presenting data on unsatisfactory rates for either ThinPrep or SurePath and utilising actual patient samples (ie, not laboratory manipulated samples) and not employing glacial acetic acid to increase the satisfactory rate. Four of these studies presented data on both ThinPrep and SurePath use in the same population by the same laboratory and were therefore included in the meta-analysis. Our contacts with industry and other researchers did not reveal additional usable studies. The selection process is summarised in figure 1.

Data extraction
Two of the authors (CN and DF) extracted data independently from the 42 studies meeting the inclusion criteria. These results were then compared and any discrepancies resolved. The following data were extracted: (1) number of patients included, (2) type of liquid-based system used (ThinPrep or SurePath), (3) per cent of unsatisfactory cases, (4) country of study, (5) year of study, (6) whether image analysis software was used to screen the slides and (7) the number of women in the study (sample size). The lack of ambiguity of the outcome measure (only two end points are possible: unsatisfactory or satisfactory), combined with the irrelevance of a follow-up (latent) period, obviated the need for quality scoring of the included studies.

Statistical analysis
Unsatisfactory rates were first compared using a univariate general linear model in SPSS V.19. The dependent variable was unsatisfactory rate, and the dependent variables were year of study (divided into 2002 and before to capture studies published before TBS revision in 2001 and 2003 and later), platform (ThinPrep vs SurePath), country where study was performed and whether image analysis software was used. Studies were weighted by the number of women participating in each one. In addition to the significance level, observed power was calculated for each variable. Differences were considered significant at an α level of 0.05. Meta-analysis was then performed using Review Manager V.4.2.7 A χ² test for heterogeneity among studies included in the meta-analysis revealed an I² of 97% with a p value of <0.00001, indicating significant

Figure 1 Selection of studies of unsatisfactory rates of cervical cytology smears prepared with ThinPrep and SurePath platforms.
heterogeneity among these studies (although the heterogeneity was quantitative rather than qualitative as all the trials demonstrated the same trend). Therefore, a random effects model was employed to calculate the pooled OR.

RESULTS
A total of 1,120,418 cervical cytology smears were reported in 14 different studies using the SurePath platform (table 1). The pooled unsatisfactory rate (weighted average) was 0.3%. For cervical cytology smears processed on the ThinPrep platform, 28 studies reported on 1,148,755 smears for a pooled unsatisfactory rate (weighted average) of 1.3% (table 2). A general linear model as previously described was employed to test for a difference in unsatisfactory rate ThinPrep and SurePath. Year of publication ($p = 0.021$) and country where research was performed ($p = 0.004$) were independent predictors of unsatisfactory rate. The use of image analysis software ($p = 0.091$) and the LBP platform used ($p = 0.558$) were not independent predictors of unsatisfactory rate. However, the observed power for LBP platform was very low at 0.087, making the risk of a type II error high. To attempt to gain statistical power, we performed a meta-analysis where we considered only studies where both platforms were evaluated on the same patient population by the same laboratory. We found three such studies in the published literature and added data from one additional unpublished study (table 3). All four of these studies reported similar populations but different patients who were screened with either ThinPrep or SurePath platform. The pooled RR from the meta-analysis was 0.44 (95% CI 0.25 to 0.77) in favour of SurePath over ThinPrep (figure 2). A Z-test for overall effect was statistically significant at $p = 0.004$.

Because of the small number of studies included in the meta-analysis, a funnel plot was not informative. However, the four included showed similar unsatisfactory rates to other studies and therefore we felt were representative of the other studies retrieved.

DISCUSSION
Despite being one of the most successful screening tests for cancer, cervical cytology smears have been criticised for low sensitivity. False-negative cervical cytology smears are responsible for this decrease in sensitivity and may result from collection errors, screening errors or interpretation errors.

We set out to examine unsatisfactory rates in LBC as these have been demonstrated to be largely reproducible within laboratories but not across laboratories. Most laboratories use TBS or some modification thereof for interpretation of cervical cytology smears. We could not, however, establish the criteria used to determine adequacy for each platform; some laboratories use the methods described in the manufacturer’s guide (TBS based), while others have adopted their own criteria and many authors do not elaborate on this in their methods. Furthermore, our results showed that year of publication and to a greater extent country were significant confounding factors in the comparison of unsatisfactory rates between ThinPrep and SurePath platforms. These confounding factors resulted in very low power to detect a statistically significant difference in unsatisfactory rates, despite a wide difference in mean unsatisfactory rates.

**Table 1 Unsatisfactory cervical cytology smear rates in populations using the SurePath platform**

<table>
<thead>
<tr>
<th>Lead author</th>
<th>Year</th>
<th>Total number of cervical cytology smears</th>
<th>Number of unsatisfactory smears</th>
<th>Percentage of unsatisfactory smears</th>
<th>Location of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colgan et al$^8$</td>
<td>2004</td>
<td>352,680</td>
<td>915</td>
<td>0.3</td>
<td>Canada</td>
</tr>
<tr>
<td>Zhao et al$^9$</td>
<td>2011</td>
<td>972</td>
<td>2</td>
<td>0.2</td>
<td>China</td>
</tr>
<tr>
<td>Kirscher et al$^{10}$</td>
<td>2006</td>
<td>84,414</td>
<td>292</td>
<td>0.3</td>
<td>Denmark</td>
</tr>
<tr>
<td>Beerman et al$^{11}$</td>
<td>2008</td>
<td>35,315</td>
<td>46</td>
<td>0.1</td>
<td>the Netherlands</td>
</tr>
<tr>
<td>Sykes et al$^{12}$</td>
<td>2008</td>
<td>451</td>
<td>12</td>
<td>2.7</td>
<td>New Zealand</td>
</tr>
<tr>
<td>Sykes et al$^{12}$</td>
<td>2008</td>
<td>457</td>
<td>12</td>
<td>2.6</td>
<td>New Zealand</td>
</tr>
<tr>
<td>Kitchener et al$^{13}$</td>
<td>2011</td>
<td>22,145</td>
<td>354</td>
<td>1.6</td>
<td>UK</td>
</tr>
<tr>
<td>Narine and Young$^{14}$</td>
<td>2007</td>
<td>53,982</td>
<td>208</td>
<td>0.4</td>
<td>UK</td>
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<td>Narine and Young$^{14}$</td>
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<td>27,738</td>
<td>327</td>
<td>1.2</td>
<td>UK</td>
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<td>Alsharif et al$^{15}$</td>
<td>2009</td>
<td>232,022</td>
<td>360</td>
<td>0.2</td>
<td>USA</td>
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<td>Stark$^{16}$</td>
<td>2007</td>
<td>137,703</td>
<td>302</td>
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<td>USA</td>
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<td>Nance$^{17}$</td>
<td>2007</td>
<td>92,875</td>
<td>158</td>
<td>0.2</td>
<td>USA</td>
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<tr>
<td>Fremont-Smith et al$^{18}$</td>
<td>2004</td>
<td>58,580</td>
<td>130</td>
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<tr>
<td>Sass$^{19}$</td>
<td>2003</td>
<td>8771</td>
<td>14</td>
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<tr>
<td>Wilbur et al$^{20}$</td>
<td>2009</td>
<td>12,313</td>
<td>27</td>
<td>0.2</td>
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<tr>
<td>Total</td>
<td></td>
<td>1,120,418</td>
<td>3,159</td>
<td>0.3</td>
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</tr>
</tbody>
</table>
Table 2  Unsatisfactory cervical cytology smear rates in populations using the ThinPrep platform

<table>
<thead>
<tr>
<th>Lead author</th>
<th>Year</th>
<th>Total number of cervical cytology smears</th>
<th>Number of unsatisfactory smears</th>
<th>Percentage of unsatisfactory smears</th>
<th>Location of study</th>
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<tr>
<td>Davey et al [1]</td>
<td>2007</td>
<td>52,665</td>
<td>795</td>
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<td>Australia</td>
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<tr>
<td>Roberts et al [2]</td>
<td>1997</td>
<td>35,560</td>
<td>235</td>
<td>0.7</td>
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<td>Shield et al [3]</td>
<td>1999</td>
<td>300</td>
<td>19</td>
<td>6.3</td>
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<tr>
<td>Halford et al [4]</td>
<td>2009</td>
<td>87,284</td>
<td>758</td>
<td>0.9</td>
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<tr>
<td>Duggan et al [5]</td>
<td>2006</td>
<td>2288</td>
<td>10</td>
<td>0.4</td>
<td>Canada</td>
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<td>Belison et al [6]</td>
<td>2002</td>
<td>1450</td>
<td>158</td>
<td>10.9</td>
<td>China</td>
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<td>Zhao et al [6]</td>
<td>2011</td>
<td>1033</td>
<td>15</td>
<td>1.5</td>
<td>China</td>
</tr>
<tr>
<td>Yeoh et al [7]</td>
<td>1999</td>
<td>16,541</td>
<td>93</td>
<td>0.6</td>
<td>Hong Kong</td>
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<tr>
<td>Cheung et al [8]</td>
<td>2003</td>
<td>190,667</td>
<td>608</td>
<td>0.3</td>
<td>Hong Kong</td>
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<td>Grace et al [9]</td>
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<td>1,000</td>
<td>13</td>
<td>1.3</td>
<td>Ireland</td>
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<tr>
<td>Treacy et al [10]</td>
<td>2009</td>
<td>41,312</td>
<td>1342</td>
<td>3.2</td>
<td>Ireland</td>
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<tr>
<td>Ronco et al [11]</td>
<td>2007</td>
<td>22,708</td>
<td>583</td>
<td>2.6</td>
<td>Italy</td>
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<td>Rahimi et al [12]</td>
<td>2008</td>
<td>467</td>
<td>9</td>
<td>1.9</td>
<td>Italy</td>
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<td>Luthra et al [13]</td>
<td>2001</td>
<td>1,024</td>
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<td>Kuwait</td>
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<td>Siebers et al [14]</td>
<td>2008</td>
<td>46,064</td>
<td>153</td>
<td>0.3</td>
<td>the Netherlands</td>
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<td>Williams [15]</td>
<td>2006</td>
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<td>1,493</td>
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<td>Scotland</td>
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<td>Taylor et al [16]</td>
<td>2006</td>
<td>3184</td>
<td>70</td>
<td>2.2</td>
<td>South Africa</td>
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<tr>
<td>Tuncer et al [17]</td>
<td>2005</td>
<td>4322</td>
<td>72</td>
<td>1.7</td>
<td>Turkey</td>
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<td>2011</td>
<td>23,436</td>
<td>456</td>
<td>1.9</td>
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<td>Alsharif et al [19]</td>
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<td>5,419</td>
<td>124</td>
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<td>USA</td>
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<td>Nance [20]</td>
<td>2007</td>
<td>88,575</td>
<td>567</td>
<td>0.6</td>
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<td>Bentz [21]</td>
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<td>Bentz [22]</td>
<td>2002</td>
<td>15,154</td>
<td>197</td>
<td>1.3</td>
<td>USA</td>
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<tr>
<td>Bolick and Hellman [23]</td>
<td>1998</td>
<td>10,694</td>
<td>31</td>
<td>0.3</td>
<td>USA</td>
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<tr>
<td>Wachtel et al [24]</td>
<td>2009</td>
<td>2,890</td>
<td>77</td>
<td>2.7</td>
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<tr>
<td>Harkness et al [25]</td>
<td>2003</td>
<td>3,000</td>
<td>80</td>
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<td>Duby and DiFurio [26]</td>
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<td>1,027</td>
<td>1.8</td>
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<td>Duby and DiFurio [27]</td>
<td>2009</td>
<td>53,209</td>
<td>783</td>
<td>1.5</td>
<td>USA</td>
</tr>
<tr>
<td>Zhao and Austin [28]</td>
<td>2009</td>
<td>222,242</td>
<td>3,230</td>
<td>1.4</td>
<td>USA</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,148,755</td>
<td>15,593</td>
<td>1.3</td>
<td></td>
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</table>

Table 3  Studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Lead author</th>
<th>Year</th>
<th>Platform</th>
<th>Total number of cervical cytology smears</th>
<th>Number of unsatisfactory smears</th>
<th>Percentage of unsatisfactory smears</th>
<th>Location of study</th>
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</thead>
<tbody>
<tr>
<td>Zhao et al [6]</td>
<td>2011</td>
<td>TP</td>
<td>972</td>
<td>2</td>
<td>1.5</td>
<td>China</td>
</tr>
<tr>
<td>Zhao et al [6]</td>
<td>2011</td>
<td>SP</td>
<td>1,033</td>
<td>15</td>
<td>0.2</td>
<td>China</td>
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<td>2011</td>
<td>TP</td>
<td>23,436</td>
<td>456</td>
<td>2.0</td>
<td>UK</td>
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<tr>
<td>Kitchener et al [18]</td>
<td>2011</td>
<td>SP</td>
<td>22,145</td>
<td>354</td>
<td>1.6</td>
<td>UK</td>
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<tr>
<td>Narine and Young [14]</td>
<td>Unpublished</td>
<td>TP</td>
<td>58,973</td>
<td>1,250</td>
<td>2.1</td>
<td>UK</td>
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<td>Narine and Young [14]</td>
<td>Unpublished</td>
<td>SP</td>
<td>27,738</td>
<td>327</td>
<td>1.2</td>
<td>UK</td>
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<td>Nance [20]</td>
<td>2007</td>
<td>TP</td>
<td>88,575</td>
<td>567</td>
<td>0.6</td>
<td>USA</td>
</tr>
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<td>Nance [20]</td>
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<td>SP</td>
<td>92,875</td>
<td>158</td>
<td>0.2</td>
<td>USA</td>
</tr>
</tbody>
</table>

SP, SurePath; TP, ThinPrep.
between the two platforms. In contrast, a meta-analysis comparing four head-to-head studies did reveal a lower unsatisfactory rate for the SurePath platform. These differences underscore the fact that multiple factors are associated with overall unsatisfactory rates with the platform used representing only one of these.

It is also acknowledged that there are other possible biases in the source literature that our analyses could not control for. These include the relative experience of the cytologists in reading slides prepared using one or the other platform and any possible undisclosed biases in the allocation of individuals to treatment groups in the four head-to-head studies. The differences in unsatisfactory rates due to LBC platform we report here are most likely a function of differences in the proprietary methodology for each platform. ThinPrep employs a filter-based technology, while SurePath uses a density/sedimentation process. Differences are also encountered when collecting the sample; ThinPrep requires the collector to rinse the collection device in the liquid media that is followed by disposal of the collection device. In contrast, the SurePath collection device is placed in the media and sent to the laboratory for processing. This difference has been demonstrated to account for up to 38% loss of the ThinPrep sample in a study by Bigras et al.44 These preparatory differences represent a significant technical difference, which laboratories must consider prior to adopting LBC. However, counterbalancing this loss of sample is the fact that ThinPrep samples are significantly less labour intensive than SurePath samples for the processing laboratory.

As tables 1 and 2 show, there was considerable variation in unsatisfactory rates among jurisdictions, with countries in the European Union in particular tending to show higher unsatisfactory rates in both studies of SurePath and ThinPrep. This is likely attributable to variations in adequacy criteria compared with TBS. This is likely attributable to the ability to perform hybrid capture human papilloma virus testing.47

The data presented here show a significant difference between the different platforms with SurePath having a significantly lower rate of unsatisfactory samples. This pattern was observed when considering different countries and methods used to determine thresholds for unsatisfactory designation. Consistent with this observation, data are from a College of American Pathologist survey reporting differences in unsatisfactory rates between laboratories using SurePath (median unsatisfactory rate 0.3%) and ThinPrep (median unsatisfactory rate 1.1%) platforms.48 These numbers are similar to the pooled unsatisfactory rates we report in this study (0.3% for SurePath and 1.3% for ThinPrep).

A limitation of our study is that it considers only one aspect of LBP platform selection (unsatisfactory rate), whereas other factors such as specificity and sensitivity must also be considered. A discussion of this is outside the scope of this paper but interested readers are referred to the meta-analysis of Arbyn et al4 for further information. The implication of this unsatisfactory rate difference is also a consideration for specimens, which could be biobanked for further studies to evaluate new biomarkers and how they may perform in unsatisfactory LBC samples.49

Unsatisfactory samples represent a missed opportunity for screening50 and are more often associated with a cervical abnormality.51 It has also been well described that patients with an invasive cervical cancer have a much greater rate of unsatisfactory Pap smears, often as a result of scant cellularity and obscuring elements such as blood and inflammation.52–54 In addition to the technical requirements of sample preparation, laboratories may wish to consider the variation in unsatisfactory sample rates when choosing an LBC platform.

**Contributors** DF, NN and CN designed the study. DF and CN collected the data. CN analysed and interpreted the data. The manuscript was prepared by DF and CN and commented on by all authors. CN is the guarantor.

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**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** Data used in this paper are available from the corresponding author.
Liquid-based cytology unsatisfactory rates

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