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## The "REACH-Bhutan" study: cervical cancer screening in rural Bhutan

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3 1 **Title: The “REACH-Bhutan” study: cervical cancer screening in rural Bhutan**  
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43 16 **Brief title:** Cervical cancer screening in rural Bhutan  
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3 **27 Abstract (words=298)**  
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5 **28 Objectives.** The Bhutanese Screening Programme recommends a Pap smear every three years for  
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8 **29** women aged 25–65 years and coverage ranges from 20% to 60%, being especially challenging in  
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11 **30** rural settings. The “REACH-Bhutan” study was conducted to assess the feasibility and outcomes  
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13 **31** of a novel approach to cervical cancer screening in rural Bhutan.

14 **32 Design.** Cross-sectional, population-based, study of cervical cancer screening based on the  
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17 **33** careHPV test on self-collected samples.

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19 **34 Setting.** Women were recruited in rural primary health care centres, i.e. Basic Health Units  
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22 **35** (BHU), across Bhutan.

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24 **36 Participants.** Overall, 3,648 women aged 30–60 years were invited from 15 BHUs differing in  
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27 **37** accessibility, size, and ethnic composition of the population.

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29 **38 Interventions.** Participants provided a self-collected cervico-vaginal sample and were  
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32 **39** interviewed. Samples were tested using careHPV in Thimphu (the Bhutanese capital) referral  
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34 **40** laboratory.

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36 **41 Main outcome measures.** Screening participation by geographic area, centre, age, and travelling  
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39 **42** time. Previous screening history and careHPV-positivity by selected characteristics of the  
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41  
42 **43** participants.

43  
44 **44 Results.** In April/May 2016, 2590 women (median age: 41 years) were enrolled. Study  
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47 **45** participation was 71% and significantly heterogeneous by BHU (range: 31%–96%). Participation  
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49  
50 **46** decreased with increase in age (81% in 30–39 year-old women but only 59% in  $\geq 50$  years), and  
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52 **47** travelling time (90% in women living  $< 30$  minutes from the BHU *versus* 62% among those  $> 6$   
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54 **48** hours away). 50% participants reported a previous screening, the proportion of never-screened  
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57 **49** women varied significantly by BHU (range: 2%–72%). 265 women (10%; 95%CI 9%–11%)  
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3 50 were *care*HPV-positive, with a significant variation by BHU (range: 5%–19%) and number of  
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5 51 sexual partners (prevalence ratio for  $\geq 3$  vs. 0–1=1.55; 95% CI: 1.05–2.27).  
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## 8 **Conclusions:**

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10 53 Community-based cervical cancer screening, testing self-collected samples, can achieve high  
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12 54 coverage in rural Bhutan. New solutions to bring self-collection, HPV testing, and precancer  
13  
14 55 treatment to the remotest villages are needed.  
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18  
19 57 **Keywords:** Cervical cancer screening; self-collection; *care*HPV; rural population; Bhutan.  
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## 22 59 **Article summary section:**

### 23 24 60 **Strengths and limitations of this study**

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28 61 • The study was conducted countrywide in a range of rural primary health care centres,  
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30 62 which varied in accessibility, size, and ethnic composition of the target population.  
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32 63 • The target population of each centre was enumerated on the basis of up-to-date and  
33  
34 64 detailed demographic surveys.  
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36 65 • A reliable local mobile data network ensured timely and effective study coordination,  
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38 66 data collection, and quality controls.  
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40 67 • The proposed diagnostic and treatment solutions presented specific challenges and were  
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42 68 less reliable than expected.  
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## 71 INTRODUCTION

72 Cervical cancer represents the most common cancer among females in Bhutan, with an age-  
73 standardised incidence rate of approximately 13 cases per 100,000 person years.<sup>1</sup> The country is  
74 strongly engaged in the prevention of cervical cancer. In the year 2000, the Ministry of Health  
75 launched a national cytology-based screening programme, and a Pap smear is currently  
76 recommended every three years to women aged 25–65 years.<sup>2</sup> In the year 2010, Bhutan was the  
77 first low/middle-income country (LMIC) to initiate a successful national vaccination programme  
78 against human papillomavirus (HPV) with >90% coverage in girls age 12–18 years.<sup>3</sup> Conversely,  
79 screening coverage is much lower and fairly heterogeneous across the country, ranging from  
80 20% to 60% of the target population in different provinces.<sup>4,5</sup> In rural areas, where approximately  
81 60% of the Bhutanese live,<sup>6</sup> cytology-based screening campaigns are occasionally conducted but  
82 coverage remains poor,<sup>4</sup> follow-up and treatment of screening-positive women challenging.  
83 Organized screening programmes are demanding in terms of administrative, human, financial,  
84 and logistic resources. Pap smear-based programmes require frequent visits, trained staff, and  
85 strict quality control. In contrast, HPV-based screening allows for longer screening intervals,<sup>7,8</sup>  
86 self-sampling,<sup>9</sup> and automation of the diagnostic procedure. It is therefore an attractive option to  
87 improve the acceptability and cost-effectiveness of screening.<sup>10</sup>  
88 In 2016, the Ministry of Health of Bhutan and the International Agency for Research on Cancer  
89 (IARC) implemented the “REACH-Bhutan” study to assess the feasibility, outcomes, and  
90 challenges of cervical cancer screening based on the *care*HPV test on self-collected samples  
91 among women 30–60 years of age in rural areas of the country.

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93

## 94 MATERIAL AND METHODS

### 95 Study population and recruitment

96 Our study targeted women aged 30–60 years living in rural areas; recruitment and sample  
97 collection took place from April to May 2016 in Basic Health Units (BHUs), the facilities that  
98 provide primary health care to the Bhutanese population. The Bhutanese principal investigator  
99 (UT) selected 15 BHUs that differed by accessibility, size, and ethnic composition of the served  
100 population (Figure 1). Lists of household members in each village were obtained from the BHU  
101 survey produced yearly for demographic purposes.

102 Local health workers (HWs) visited the villages served by the selected BHUs to invite  
103 eligible women to come to the BHU to participate in the study on specified dates. The benefits of  
104 cervical cancer screening and the purposes of the study were explained to the women during  
105 public invitation sessions. Women from the same village were invited to attend screening at the  
106 BHUs on the same date. Pregnant women, women with mental disability, who had undergone  
107 hysterectomy or planned to leave the study area in the next 6 months were not eligible.

108 On the appointment date, two or three HWs and one of the two mobile study teams (one  
109 for East and one for West Bhutan, each composed of two nurses and supervised by a  
110 gynaecologist) provided additional information on the study, collected an informed consent  
111 form, and administered a short electronic questionnaire on the BHU's premises. The entire  
112 process required less than 20 minutes and certain BHUs were able to manage more than 100  
113 women per day. Whenever possible, the recently introduced national citizenship identification  
114 number (CID), which uniquely identifies Bhutanese citizens, and at least one mobile telephone  
115 number were recorded for follow-up purposes.

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### 117 Sample collection, transportation, and laboratory analysis

118 Each participant was asked to provide a self-collected cervico-vaginal sample using a  
119 *careBrush*. They were instructed to insert the brush deep into the vagina and rotate it 3 to 5 times  
120 before dipping it in a tube containing *careHPV* collection medium. Tubes were then stored in  
121 fridges until they were transported in cool boxes to the central laboratory of Jigme Dorji  
122 Wangchuck National Referral Hospital (JDWNRH) in Thimphu. Samples were stored at ~4° C  
123 and an aliquot was tested using the *careHPV* platform (Qiagen Corporation, Gaithersburg, MD,  
124 USA) according to the manufacturer's instructions. The *careHPV* test is a validated signal-  
125 amplification, rapid batch diagnostic test for the detection of DNA of 13 high risk (HR) HPV  
126 types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and HPV66.<sup>11</sup> *careHPV* results were  
127 communicated as soon as possible to each BHU to arrange follow-up of *careHPV*-positive  
128 women and of a fraction of *careHPV*-negative women, as a quality control measure.

### 129 Data collection and statistical analyses

130 All information on study participants and biological samples were collected and stored on  
131 portable electronic devices. Whenever a mobile data network was accessible, the stored data  
132 were uploaded to the IARC server and portable devices were synchronized with the most recent  
133 version of the study database. The distribution of the target population in each BHU by age  
134 group and by village of residence was obtained from the demographic survey conducted in year  
135 2015. Travelling time from village of residence to the corresponding BHU was estimated for  
136 each woman. On account of the socio-geographic characteristics of the study areas, most women  
137 had to reach the BHU on foot. We subdivided the travelling time into seven categories (i.e. <30  
138 minutes, 30 to 59 minutes, 1 hour to 1 hour 59 minutes, 2 hours to 2 hours 59 minutes, 3 hours to  
139 3 hours 59 minutes, 4 hours to 5 hours 59 minutes, and 6 or more hours), and fitted a mixed-



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3 140 effect logistic model to data to assess the influence of travelling time on study participation, with  
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5 141 BHUs as clusters.

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7 142 Among participating women, we assessed prevalence ratios (PR) and corresponding 95%  
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9 143 confidence intervals (CI) for lack of previous cervical cancer screening and *careHPV* positivity  
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11 144 according to selected characteristics using binomial regression models with a log link and  
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13 145 adjustment for age group (30–39, 40–49, and  $\geq 50$  years) and BHU of recruitment, as appropriate.  
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15 146 For each variable of interest, missing or undisclosed (i.e. labelled as “prefer not to answer”)  
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17 147 information were treated as not informative and excluded from the analyses.

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21 148 The outcome of follow-up and clinical management of *careHPV*-positive women will be  
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23 149 reported in a future publication.

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## 27 28 151 **RESULTS**

29  
30 152 Out of 15 BHUs included in “REACH-Bhutan”, 6 are located in West Bhutan and 9 in  
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32 153 East Bhutan (Figure 1). They serve a total of 3,648 women age 30–60 years (Figure 2). Overall  
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34 154 participation was 71% (95% CI: 69.5%–72.5%) and was similar in the West and the East. It  
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36 155 was, however, significantly heterogeneous by BHU (range: 31%–96%, I-square 99%,  $p < 0.001$ ),  
37  
38 156 and age group (81% in 30–39 year-old women but only 59% in  $\geq 50$  years). Participation steadily  
39  
40 157 decreased with the increase in travelling time from village to BHU being 90% (95% CI: 84%–  
41  
42 158 94%) for women living less than 30 minutes from the BHU but 62% (95% CI: 50%–73%)  
43  
44 159 among those 6 hours away or more (see appendix p1). The influence of travelling time strongly  
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46 160 increased with a woman’s age: the drop in participation between 30 minutes and 6 hours was  
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48 161 from 93% (95% CI: 87%–96%) to 76% (95% CI: 64%–84%) among women 30–39 years old,  
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50 162 but from 86% (95% CI: 75%–92%) to 45% (95% CI: 30%–62%) among women  $\geq 50$  years  
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3 163 (Figure 3). The village of residence was not reported by 6 women or did not belong to the BHU  
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5 164 catchment area (7 women). These women did not contribute to the analysis reported in Figure 3.

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8 165 A total 2,590 women accepted the invitation and came to a BHU (median age: 41 years;  
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10 166 inter-quartile range: 35 to 49 years). Ninety-nine percent belonged to 4 ethnic groups: Sarchop  
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12 167 (55%); Lhotsampa (27%); Ngalop (13%); and Khengpa (4%), each group predominating in at  
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14 168 least one BHU (Figure 1). All but two women provided a telephone number and 60% provided  
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16 169 their identity card number. Most women stated that self-sampling was easy to perform (96%) and  
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18 170 painless (90%). Macroscopic blood traces were observed in 3.5% of sample of non-menstruating  
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20 171 women (data not shown).

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23 172 Fifty percent of participants reported having had previous screening (Figure 4A) and, among  
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25 173 them, 83% had had a Pap smear in the last 4 years (data not shown). The proportion of never-  
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27 174 screened women varied across individual BHUs (range: 2%–72%, I<sup>2</sup> = 99%, P-value<0.001).  
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29 175 Table 1 shows the characteristics that were significantly associated with lack of screening, i.e.,  
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31 176 age group (PR for  $\geq 50$  vs. 30–39 years =1.36; 95% CI: 1.26–1.47); region (PR for West vs.  
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33 177 East=2.84; 95% CI: 2.05–3.95); travelling time from village to BHU (PR for  $\geq 6$  hours vs. <1  
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35 178 hour =1.53; 95% CI: 1.38–1.69); ethnicity (PR vs. Sarchop = 1.65; 95% CI: 1.52–1.80 for  
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37 179 Ngalop; 1.41; 95% CI: 1.29–1.53 for Lhotsampa; and 0.58; 95% CI: 0.41–0.81 for Khengpa);  
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39 180 educational level (PR for literate vs. illiterate =0.85; 95% CI: 0.73–0.99); occupation (PR for  
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41 181 shopkeepers/saleswoman/manual worker vs. farmer/housewives =0.56; 95% CI: 0.34–0.90);  
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43 182 marital status (PR for never married vs. married = 1.35; 95% CI: 1.07–1.71); and nulliparity (PR  
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45 183 for 0 vs.  $\geq 3$  = 1.25; 95% CI: 1.05–1.49). Lifetime number of sexual partners, age at first sexual  
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47 184 intercourse, and *careHPV* positivity were unrelated to screening history (Table 1).  
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3 185 Overall, 265 women (10%; 95% CI 9%–11%) were *care*HPV-positive with a significant  
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5 186 variation by BHU (range: 5%–19%,  $I^2 = 63%$ ,  $P\text{-value} < 0.001$ ) (Figure 4B). Table 2 shows the  
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7 187 relationship between *care*HPV positivity and various women’s characteristics. Significant risk  
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9 188 factors for HPV positivity included region of Bhutan (PR for West vs. East = 0.55; 95% CI:  
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11 189 0.30–1.00), marital status (PR for widow, separated or divorced vs. married = 1.71; 95% CI: 1.21–  
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13 190 2.41), number of pregnancies (PR for 1–2 vs.  $\geq 3 = 1.49$ ; 95% CI: 1.15–1.93), and lifetime  
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15 191 number of sexual partners (PR for  $\geq 3$  vs. 0–1 = 1.55; 95% CI: 1.05–2.27). *care*HPV positivity  
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17 192 was not significantly associated with age, ethnicity, educational level, occupation, age at  
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19 193 first sexual intercourse, and lack of previous screening (Table 2).  
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## 27 195 **DISCUSSION**

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29 196 The findings from “REACH-Bhutan” show that community-based cervical cancer  
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31 197 screening using self-collected samples and *care*HPV test is feasible in BHUs and can achieve  
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33 198 high-coverage in rural Bhutan.  
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36 199 Seventy percent of women from rural communities responded favourably to the invitation  
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38 200 to come to their BHU to undergo HPV screening. In comparison, in Thimphu, the Bhutanese  
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40 201 capital, only 33% (95% CI: 29–37) of invited women of the same age group accepted to  
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42 202 participate in a similar study.<sup>5</sup> However, participation significantly decreased with increasing age  
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44 203 and travelling time between the village of residence and the BHU. The negative effect of living  
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46 204 far away from a BHU was especially strong among older women. Furthermore, older age and  
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48 205 large distance from BHUs were confirmed to be risk factors for lack of previous screening  
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50 206 among the women who participated in our present study (Table 1).  
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3 207 The large majority of study participants reported to be illiterate farmers or housewives,  
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5 208 currently married and sexually active. One-fifth reported two sexual partners or more, and 74%  
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7 209 three children or more. Among study participants, 50% had never been screened before,  
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9 210 confirming that rural areas are underserved compared to Thimphu, where 33% (95% CI: 30–36)  
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11 211 of 30–60 year-old study participants had never been screened.<sup>5</sup> Despite the remarkable socio-  
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13 212 demographic homogeneity of the rural communities included, participation in “REACH-Bhutan”  
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15 213 and history of previous screening among participating women were significantly different among  
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17 214 BHUs pointing to different levels of success in application of the national guidelines.

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19 215 The varying degree of participation in our current study and of previous screening across  
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21 216 BHUs may be also related to differences in ethnic composition. Indeed, lack of previous  
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23 217 screening was significantly more frequent among women who belonged to the Lhotsampa  
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25 218 (mostly Hindus) and Ngalop (mostly Buddhist) ethnic groups. It is, however, unclear whether  
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27 219 Lhotsampa and Ngalop were more reluctant to be screened or lived in areas where BHUs were  
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29 220 less committed to screening. For example, in the large BHU of Bara, at the western border with  
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31 221 India, there was a suggestion that a historical absence of female HWs had had a negative impact  
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33 222 on cervical screening attendance. The few literate women and those who were shopkeepers or  
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35 223 manual workers reported more screening attendance.

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37 224 Ten percent of women were *care*HPV-positive, i.e. a percentage only slightly lower than  
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39 225 that found in Thimphu in the same age group, i.e. 14.1% (95% CI: 12.0–16.4).<sup>12</sup> Lifetime  
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41 226 number of sexual partners, being widowed, separated or divorced, and having had 1 or 2 children  
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43 227 (as compared to 3) were significantly associated with HPV positivity as reported in previous  
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45 228 IARC HPV surveys.<sup>13,14</sup> Women in West Bhutan were less likely to be HPV positive than their  
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47 229 counterparts in the east of the country and this finding is likely to reflect differences in lifestyle

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3 230 sexual habits across rural communities or ethnic groups. In fact, the percentage of women who  
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5 231 reported two or more sexual partners was 15% in the West versus 26% in the East.

7 232 The main strengths of the present study are the inclusion of a large number of women  
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9 233 from many rural villages and the relatively high and accurately estimated participation of invited  
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11 234 30–60 year-old women. Study implementation was also characterised by logistic and  
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13 235 technological challenges. We developed an mHealth platform and relied on the local mobile data  
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15 236 network to ensure a timely and effective coordination of BHU HWs and mobile study teams  
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17 237 across Bhutan, and to manage data collection, transmission, and real-time quality controls.<sup>15,16</sup>  
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19 238 Furthermore, virtually all study participants had access to at least one mobile phone, greatly  
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21 239 simplifying their recall for follow-up visits. The proposed diagnostic and treatment solutions also  
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23 240 presented specific challenges. For example, while our study demonstrated the excellent  
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25 241 acceptability and feasibility of organized screening based on self-collection, the *careHPV*  
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27 242 platform turned out to be less reliable than expected and, even after completion of the initial  
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29 243 training period, there still continued to be substantial wastage due to invalid *careHPV* runs. In  
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31 244 addition, the original plan of rapidly recalling women and offering them triage and, if necessary,  
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33 245 cryotherapy in one additional visit was not possible due to the hardship of roads and the frequent  
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35 246 malfunctioning of cryotherapy in Bhutan.

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37 247 A three-visit follow-up protocol is still ongoing and will be reported upon in a future  
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39 248 publication. At end December 2016, 248 (94%) *careHPV* positive women had had a follow-up  
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41 249 visit and 208 had undergone either cryotherapy (n=85) or loop electrosurgical excision procedure  
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43 250 (LEEP, n=123). However, due to the heavy workload in the Pathology Department, the follow-  
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45 251 up of women potentially in need of additional treatment is still incomplete.

## 53 252 **CONCLUSION**

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3 253 The “REACH-Bhutan” study shows both the deep engagement of the Ministry of Health  
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5 254 and HWs, and the willingness and resilience of Bhutanese women to comply with cervical  
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8 255 cancer screening recommendations. It also highlights, however, the need to find new solutions to  
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10 256 specific challenges, such as bringing self-collection closer to women, especially older ones living  
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12 257 in the remotest areas, possibly in coordination with the decentralized offer of other primary  
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14 258 health care activities, e.g., child vaccination, which is regularly brought from BHU to villages.  
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17 259 Also, we underscore the need to assess the reliability of technological alternatives to the  
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19 260 *careHPV* platform,<sup>17</sup> and to cryotherapy and LEEP,<sup>18</sup> for the treatment of precancerous lesions in  
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21 261 countries such as Bhutan.<sup>19</sup>  
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## 270 **Contributors**

271 IB, ST, SF, GC, and UT conceived and designed the study. IB, SF, GC, and UT drafted  
272 the manuscript. ST, TC, FL, VT, and MP critically revised the manuscript. All authors  
273 substantially contributed to the acquisition, analysis, and interpretation of data and approved the  
274 final manuscript.

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## 278 **Disclaimer**

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## 281 **Competing interests**

282 None declared.

## 283 **Ethics approval**

284 The present study had the approval of both the Research Ethical Board of the Bhutan  
285 Ministry of Health and the IARC Ethics Committee.

## 286 **Provenance and peer review**

287 Not commissioned; externally peer reviewed.

## 288 **Data sharing statement**

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289 No additional data are available.

For peer review only



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3 **290 References**  
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- 5 291 1. Ervik M, Lam F, Ferlay J, Mery L, Soerjomataram I, Bray F. Cancer Today. 2016.  
6  
7 <http://gco.iarc.fr/today> [accessed 11 November 2016].  
8 292  
9  
10 293 2. Dhendup T, Tshering P. Cervical cancer knowledge and screening behaviors among female  
11  
12 294 university graduates of year 2012 attending national graduate orientation program, Bhutan. *BMC*  
13  
14 295 *Womens Health* 2014; **14**(1): 44.  
15  
16 296 3. Dorji T, Tshomo U, Phuntsho S, et al. Introduction of a National HPV vaccination program into  
17  
18 297 Bhutan. *Vaccine* 2015; **33**(31): 3726-30.  
19  
20 298 4. Ministry of Health. National Health Survey. Thimphu, Bhutan: Ministry of Health 2012.  
21  
22 299 5. Baussano I, Tshomo U, Clifford GM, Tenet V, Tshokey T, Franceschi S. Cervical cancer screening  
23  
24 300 program in Thimphu, Bhutan: population coverage and characteristics associated with screening  
25  
26 301 attendance. *Bmc Womens Health* 2014; **14**: 147.  
27  
28 302 6. The World Bank. Rural population (% of total population).  
29  
30 <http://data.worldbank.org/indicator/SP.RUR.TOTL.ZS?locations=BT> [accessed 11 January 2017].  
31  
32 303  
33  
34 304 7. Arbyn M, Anttila A, Jordan J, et al. European Guidelines for Quality Assurance in Cervical Cancer  
35  
36 305 Screening. Second edition--summary document. *Ann Oncol* 2010; **21**(3): 448-58.  
37  
38 306 8. Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive  
39  
40 307 cervical cancer: follow-up of four European randomised controlled trials. *Lancet* 2014; **383**(9916): 524-  
41  
42 308 32.  
43  
44 309 9. Arrossi S, Thouyaret L, Herrero R, et al. Effect of self-collection of HPV DNA offered by  
45  
46 310 community health workers at home visits on uptake of screening for cervical cancer (the EMA study): a  
47  
48 311 population-based cluster-randomised trial. *Lancet Glob Health* 2015; **3**(2): e85-94.  
49  
50 312 10. Tsu V, Jeronimo J. Saving the World's Women from Cervical Cancer. *N Engl J Med* 2016; **374**(26):  
51  
52 313 2509-11.  
53  
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2  
3 314 11. Qiao YL, Sellors JW, Eder PS, et al. A new HPV-DNA test for cervical-cancer screening in  
4  
5 315 developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet Oncol* 2008; **9**(10):  
6  
7 316 929-36.  
8  
9  
10 317 12. Tshomo U, Franceschi S, Dorji D, et al. Human papillomavirus infection in Bhutan at the moment  
11  
12 318 of implementation of a national HPV vaccination programme. *BMC Infect Dis* 2014; **14**: 408.  
13  
14 319 13. Vaccarella S, Franceschi S, Herrero R, et al. Sexual behavior, condom use, and human  
15  
16 320 papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys. *Cancer Epidemiol*  
17  
18 321 *Biomarkers Prev* 2006; **15**(2): 326-33.  
19  
20  
21 322 14. Vaccarella S, Herrero R, Dai M, et al. Reproductive factors, oral contraceptive use, and human  
22  
23 323 papillomavirus infection: pooled analysis of the IARC HPV prevalence surveys. *Cancer Epidemiol*  
24  
25 324 *Biomarkers Prev* 2006; **15**(11): 2148-53.  
26  
27  
28 325 15. Hall CS, Fottrell E, Wilkinson S, Byass P. Assessing the impact of mHealth interventions in low-  
29  
30 326 and middle-income countries--what has been shown to work? *Glob Health Action* 2014; **7**: 25606.  
31  
32 327 16. Howitt P, Darzi A, Yang GZ, et al. Technologies for global health. *Lancet* 2012; **380**(9840): 507-35.  
33  
34 328 17. Cubie HA, Morton D, Kawonga E, et al. HPV prevalence in women attending cervical screening in  
35  
36 329 rural Malawi using the cartridge-based Xpert(R) HPV assay. *J Clin Virol* 2016; **87**: 1-4.  
37  
38  
39 330 18. Dolman L, Sauvaget C, Muwonge R, Sankaranarayanan R. Meta-analysis of the efficacy of cold  
40  
41 331 coagulation as a treatment method for cervical intraepithelial neoplasia: a systematic review. *BJOG*  
42  
43 332 2014; **121**(8): 929-42.  
44  
45  
46 333 19. Viviano M, Kenfack B, Catarino R, et al. Feasibility of thermocoagulation in a screen-and-treat  
47  
48 334 approach for the treatment of cervical precancerous lesions in sub-Saharan Africa. *Bmc Womens Health*  
49  
50 335 2017; **17**(1): 2.  
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338 **Table 1: Prevalence ratios (PR) for lack of previous cervical cancer screening and**  
 339 **corresponding 95% confidence intervals (CI) according to selected characteristics, Bhutan,**  
 340 **2016**

Characteristic	N tested	Never screened N (%)	Adjusted PR <sup>*</sup>	95% CI
<b>Age (years)</b>				
30–39	1139	497 (43.6)	1	–
40–49	818	407 (49.8)	1.14	1.05–1.24
≥50	633	383 (60.5)	1.36	1.26–1.47
$\chi^2_1$ for trend			<i>p</i> <0.001	
<b>Region</b>				
East	1500	625 (41.7)	1	–
West	1090	662 (60.7)	2.84	2.05–3.95
<b>Travel time from village to BHU (hours)<sup>†</sup></b>				
<1	656	285 (43.5)	1	–
1–5	1287	576 (44.8)	1.01	0.91–1.12
Missing	6	4 (66.7)	–	–
≥6–	641	422 (65.8)	1.53	1.38–1.69
$\chi^2_1$ for trend			<i>p</i> <0.001	
<b>Ethnicity<sup>†</sup></b>				
Scharchop	1435	615 (42.9)	1	–
Ngalop	340	236 (69.4)	1.65	1.52–1.80
Lhotsampa	686	401 (58.5)	1.41	1.29–1.53
Khengpa	113	26 (23.0)	0.58	0.41–0.81
Other	16	9 (56.3)	1.49	0.97–2.31
<b>Education level</b>				
Illiterate	2372	1191 (50.2)	1	–
Literate	218	96 (44.0)	0.85	0.73–0.99
<b>Current occupation</b>				
Farmer/ housewife	2488	1254 (50.4)	1	–
Shopkeeper/saleswoman/manual worker	53	12 (22.6)	0.56	0.34–0.90
Clerical staff/teacher/health worker/nun	49	21 (42.9)	0.97	0.72–1.31
<b>Marital status<sup>†</sup></b>				
Married/living as married	2390	1175 (49.2)	1	–

Never married	21	16 (76.2)	1.35	1.07–1.71
Widow/separated/divorced	179	96 (53.6)	1.05	0.92–1.21
<b>Number of pregnancies<sup>†</sup></b>				
0	67	43 (64.2)	1.25	1.05–1.49
1–2	604	285 (47.2)	1.03	0.94–1.14
≥3	1919	959 (50.0)	1	–
$\chi^2_1$ for trend				<i>p</i> =0.057
<b>Lifetime number of sexual partners</b>				
0–1	2020	983 (48.7)	1	–
2	341	166 (48.7)	0.97	0.88–1.08
≥3	214	126 (58.9)	0.98	0.88–1.09
Prefer not to answer	15	12 (80.0)	–	–
$\chi^2_1$ for trend				<i>p</i> =0.601
<b>Age at first sexual intercourse (years)<sup>‡</sup></b>				
9–14	245	124 (50.6)	1	–
15–16	515	235 (45.6)	0.93	0.81–1.06
17–19	968	452 (46.7)	1.00	0.89–1.12
≥20	707	365 (51.6)	1.02	0.91–1.15
Prefer not to answer / unknown	143	101 (70.6)	–	–
$\chi^2_1$ for trend				<i>p</i> =0.151
<b>HPV infection</b>				
Negative	2325	1168 (50.2)	1	–
Positive	265	119 (44.9)	1.01	0.91–1.13

341 CI=confidence interval; HPV=human papillomavirus; PR=prevalence ratio. \*Adjusted for age (3 classes: 30–39; 40–49; 50+) and  
 342 Basic Health Unit as appropriate. †Adjusted for age only – when adjusted for BHU, model does not converge. ‡Among sexually  
 343 active women.

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346 **Table 2: Prevalence ratios (PR) for high-risk human papillomavirus (HPV) positivity and**  
 347 **corresponding 95% confidence intervals (CI) according to selected characteristics, Bhutan,**  
 348 **2016**

Characteristic	N tested	care-HPV positive N (%)	Adjusted PR*	95% CI
<b>Age (years)</b>				
30–39	1139	129 (11.3)	1	–
40–49	818	76 (9.3)	0.80	0.62–1.05
≥50	633	60 (9.5)	0.79	0.59–1.05
$\chi^2_1$ for trend			$p=0.073$	
<b>Region</b>				
East	1500	173 (11.5)	1	–
West	1090	92 (8.4)	0.55	0.30–1.00
<b>Ethnicity</b>				
Scharchop	1435	164 (11.4)	1	–
Ngalop	340	28 (8.2)	0.68	0.31–1.49
Lhotsampa	686	58 (8.5)	0.67	0.33–1.38
Khengpa	113	15 (13.3)	1.80	0.31–10.5
Other	16	0 (0)	–	–
<b>Education level</b>				
Illiterate	2372	238 (10.0)	1	–
Literate	218	27 (12.4)	1.33	0.90–1.95
<b>Current occupation</b>				
Farmer/ housewife	2488	253 (10.2)	1	–
Shopkeeper/saleswoman/manual worker	53	3 (5.7)	0.56	0.18–1.68
Clerical staff/teacher/health worker/nun	49	9 (18.4)	1.65	0.90–3.01
<b>Marital status</b>				
Married/living as married	2390	232 (9.7)	1	–
Never married	21	3 (14.3)	1.53	0.54–4.38
Widow/separated/divorced	179	30 (16.8)	1.71	1.21–2.41
<b>Number of pregnancies</b>				
0	67	8 (11.9)	1.29	0.66–2.49
1–2	604	83 (13.7)	1.49	1.15–1.93

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3	≥3	1919	174 (9.1)	1	–
4	$\chi_1^2$ for trend			$p=0.007$	
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7	<b>Lifetime number of sexual partners</b>				
8	0–1	2020	198 (9.8)	1	–
9	2	341	36 (10.6)	1.20	0.85–1.69
10	≥3	214	31 (14.5)	1.55	1.05–2.27
11	Prefer not to answer	15	0 (0.0)	–	–
12	$\chi_1^2$ for trend			$p=0.022$	
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15	<b>Age at first sexual intercourse (years)†</b>				
16	9–14	245	21 (8.6)	1	–
17	15–16	515	48 (9.3)	1.05	0.64–1.71
18	17–19	968	109 (11.3)	1.20	0.76–1.89
19	≥20	707	72 (10.2)	1.11	0.69–1.79
20	Prefer not to answer / unknown	143	14 (9.8)	–	–
21	$\chi_1^2$ for trend			$p=0.576$	
22					
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25	<b>History of PAP smear (years)</b>				
26	Ever	1303	146 (11.2)	1	–
27	Never	1287	119 (9.3)	1.06	0.81–1.39
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349 CI=confidence interval; HPV=human papillomavirus; PR=prevalence ratio.\*Adjusted for age (3 classes: 30–39; 40–49; 50+) and  
 350 Basic Health Unit as appropriate. †Among sexually active women.

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3 352 **Figure Legends**  
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8 354 Figure 1: Map of Bhutan with study sites and predominant ethnic groups.\*  
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10 355 The size of each dot is proportional to the size of the target population of each centre.  
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14 357 Figure 2: Participation (%) and corresponding 95% confidence intervals by Basic Health Unit,  
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16 region, and age group, Bhutan, 2016.  
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21 360 Figure 3: Effect of travel time (on foot) on participation in REACH Bhutan, by age group,  
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23 Bhutan, 2016.  
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28 363 Figure 4: Percent of A) lack of previous cervical cancer screening; and B) *care*-HPV positivity  
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30 by Basic Health Unit and overall in rural areas and in Thimphu, Bhutan, 2016.  
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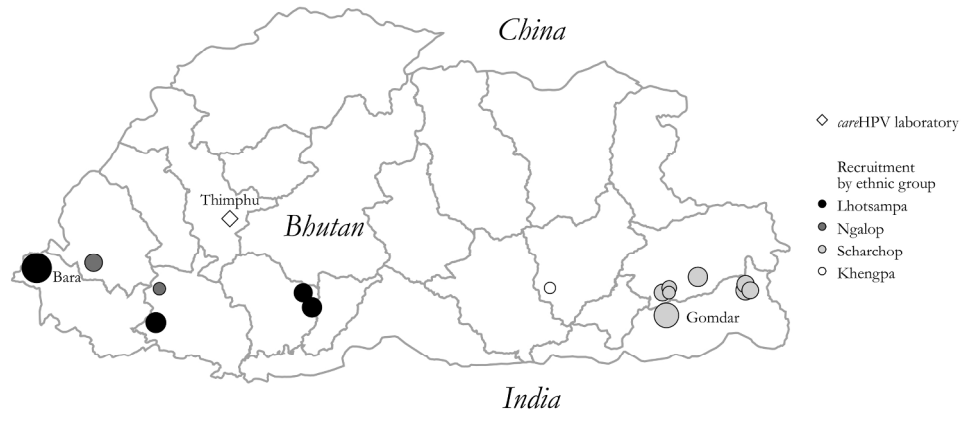


Figure 1: Map of Bhutan with study sites and predominant ethnic groups.\*  
The size of each dot is proportional to the size of the target population of each centre.

233x165mm (300 x 300 DPI)



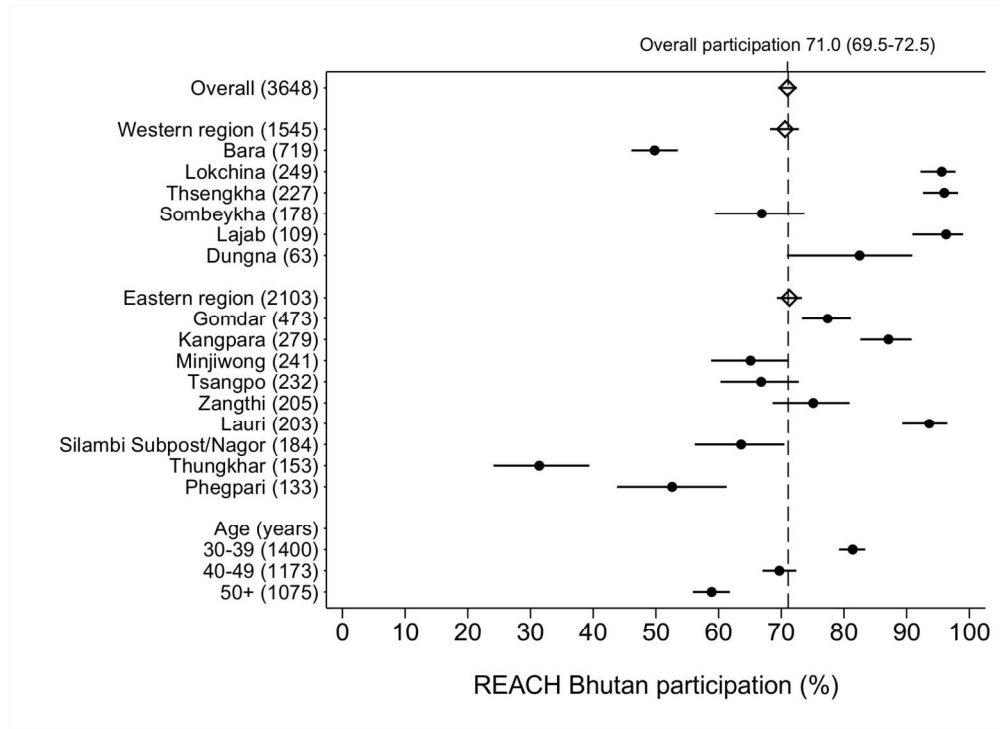


Figure 2: Participation (%) and corresponding 95% confidence intervals by Basic Health Unit, region, and age group, Bhutan, 2016.

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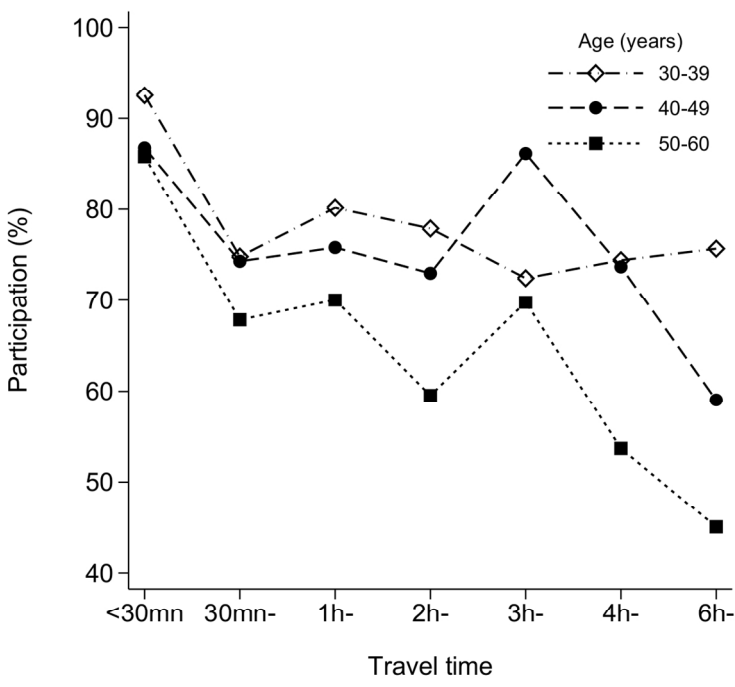


Figure 3: Effect of travel time (on foot) on participation in REACH Bhutan, by age group, Bhutan, 2016.

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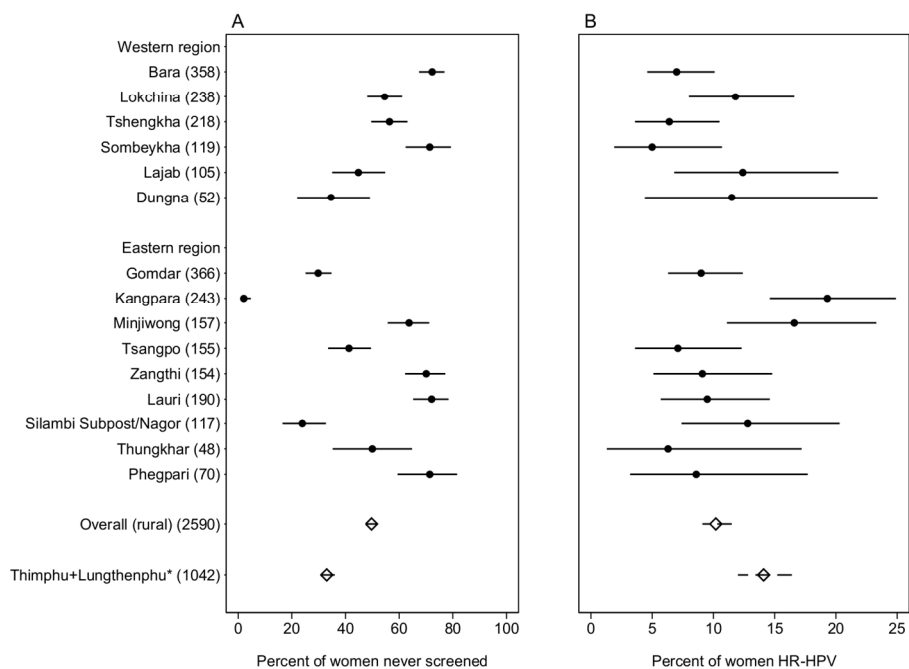
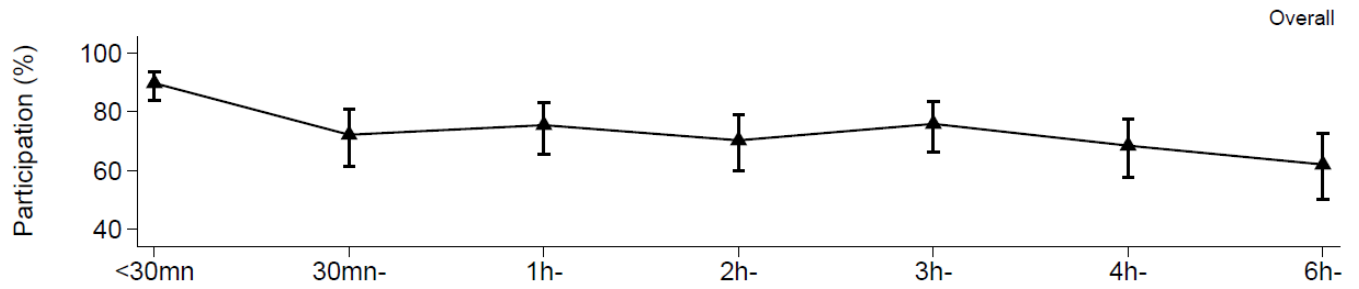


Figure 4: Percent of A) lack of previous cervical cancer screening; and B) care-HPV positivity by Basic Health Unit and overall in rural areas and in Thimphu, Bhutan, 2016.\*women aged 30-60 years in Tshomo et al 2014.

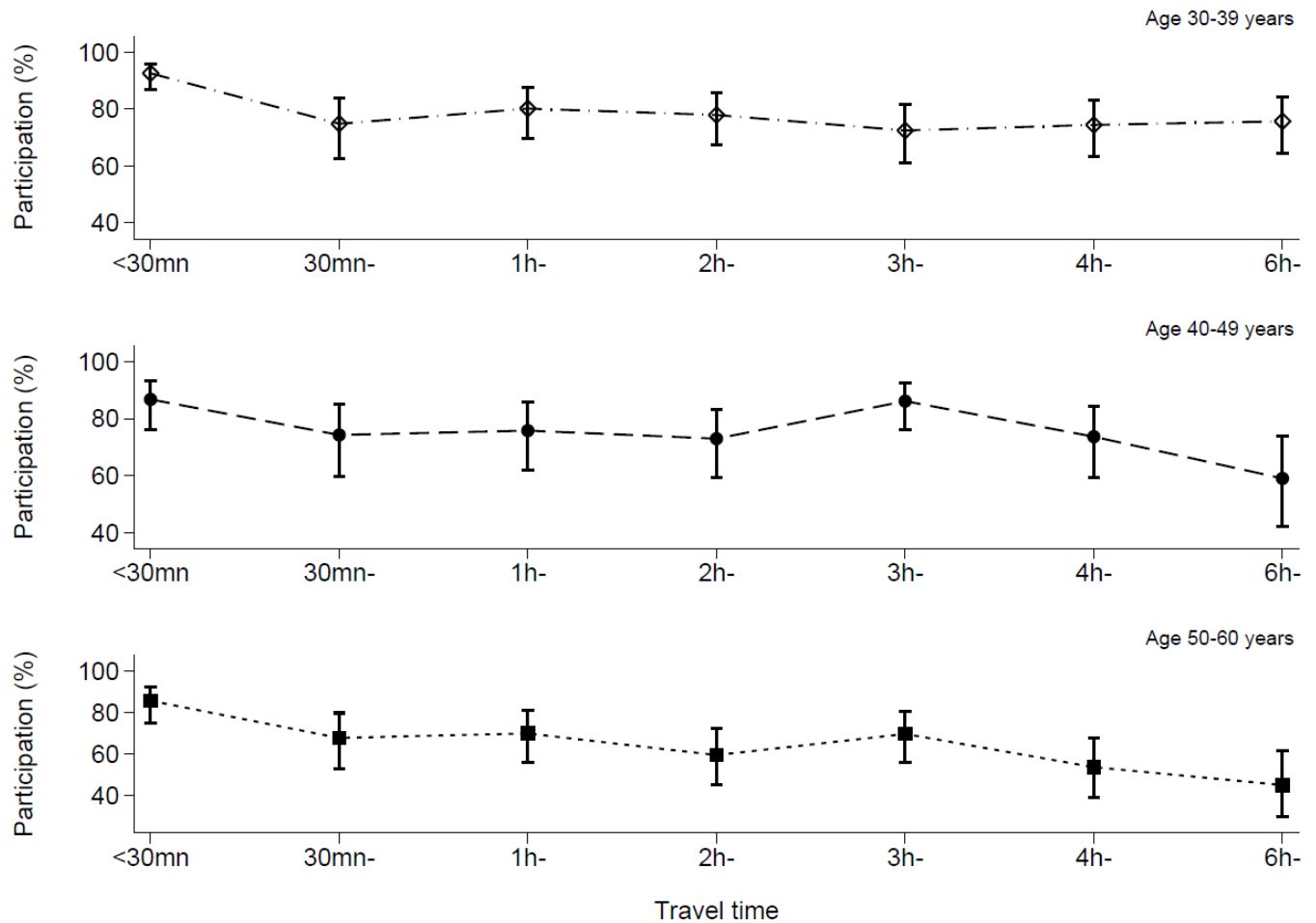
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**Appendix Figure 1: Effect of travel time on participation (%) in REACH Bhutan, A) overall, B) by age group with 95% confidence interval, Bhutan, 2016**

**A**



**B**



STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1/3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	8
		(d) If applicable, describe analytical methods taking account of sampling strategy	7
		(e) Describe any sensitivity analyses	NA
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Fig 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9; tables 1 & 2
		(b) Indicate number of participants with missing data for each variable of interest	9, tables 1 & 2
Outcome data	15*	Report numbers of outcome events or summary measures	9, Figure 2,4 and Tables
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted	9

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 1 & 2
		(b) Report category boundaries when continuous variables were categorized	Tables 1 & 2
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Figure 3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8, Figure 3
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Cervical cancer screening in rural Bhutan with the careHPV test on self-collected samples: an ongoing cross-sectional, population-based study (REACH-Bhutan)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016309.R1
Article Type:	Research
Date Submitted by the Author:	31-Mar-2017
Complete List of Authors:	Baussano, Iacopo; International Agency for Research on Cancer,, Tshering, Sangay; Dewanhang Hospital Choden, Tashi; Jigme Dorji Wangchuck National Referral Hospital Lazzarato, Fulvio; International Agency for Research on Cancer, Tenet, Vanessa; International Agency for Research on Cancer, Plummer, Martyn; International Agency for Research on Cancer, Franceschi, Silvia; International Agency for Research on Cancer,, ; Dr Clifford, G; International Agency for Research on Cancer Tshomo, Ugyen; Jigme Dorji Wangchuck National Referral Hospital
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Public health
Keywords:	Cervical cancer screening, self-collection, careHPV, rural population, Bhutan

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3 1 **Title: Cervical cancer screening in rural Bhutan with the *care*HPV test on self-collected**  
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5 2 **samples: an ongoing cross-sectional, population-based study (REACH-Bhutan)**  
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47 17 **Brief title: Cervical cancer screening in rural Bhutan**  
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10 22 Main text word count: approx. 2565 (limit 4000 words).

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15 24 Number of references: 24.

16  
17 25 Tables: 2; Figures: 4

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3 28 **Abstract (words=300)**  
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5 29 **Objectives.** The Bhutanese Screening Programme recommends a Pap smear every three years for  
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8 30 women aged 25–65 years, and coverage ranges from 20% to 60%, being especially challenging  
9  
10 31 in rural settings. The “REACH-Bhutan” study was conducted to assess the feasibility and  
11  
12 32 outcomes of a novel approach to cervical cancer screening in rural Bhutan.

13 33 **Design.** Cross-sectional, population-based study of cervical cancer screening based on the  
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17 34 *careHPV* test on self-collected samples.

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20 35 **Setting.** Women were recruited in rural primary health care centres, i.e. Basic Health Units  
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22 36 (BHU), across Bhutan.

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24 37 **Participants.** Overall, 3,648 women aged 30–60 were invited from 15 BHUs differing in  
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27 38 accessibility, size, and ethnic composition of the population.

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29 39 **Interventions.** Participants provided a self-collected cervico-vaginal sample and were  
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32 40 interviewed. Samples were tested using *careHPV* in Thimphu (the Bhutanese capital) referral  
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34 41 laboratory.

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36 42 **Main outcome measures.** Screening participation by geographic area, centre, age, and travelling  
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38  
39 43 time. Previous screening history and *careHPV*-positivity by selected characteristics of the  
40  
41 44 participants.

42  
43 45 **Results.** In April/May 2016, 2590 women (median age: 41) were enrolled. Study participation  
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45  
46 46 was 71% and significantly heterogeneous by BHU (range: 31%–96%). Participation decreased  
47  
48 47 with increase in age (81% in 30–39 year-old women; 59% in  $\geq 50$  years), and travelling time  
49  
50 48 (90% in women living  $< 30$  minutes from the BHU *versus* 62% among those  $> 6$  hours away).  
51  
52 49 50% participants reported no previous screening, with the proportion of never-screened women  
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54  
55 50 varying significantly by BHU (range: 2%–72%). 265 women (10%; 95%CI 9%–11%) were  
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4 51 *care*HPV-positive, with a significant variation by BHU (range: 5%–19%) and number of sexual  
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6 52 partners (prevalence ratio for  $\geq 3$  vs. 0–1=1.55; 95% CI: 1.05–2.27).

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8 53 **Conclusions:**

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10 54 Community-based cervical cancer screening by testing self-collected samples for HPV can  
11  
12 55 achieve high coverage in rural Bhutan. However, solutions to bring self-collection, HPV testing,  
13  
14 56 and precancer treatment even closer to the remotest villages are needed.  
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19  
20 58 **Keywords:** Cervical cancer screening; self-collection; *care*HPV; rural population; Bhutan.  
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24  
25 60 **Article summary section:**

26  
27 61 **Strengths and limitations of this study**

- 28  
29 62 • The study was conducted countrywide in a range of rural primary health care centres,  
30  
31 63 which varied in accessibility, size, and ethnic composition of the target population.  
32  
33 64 • The target population of each centre was enumerated on the basis of up-to-date and  
34  
35 65 detailed demographic surveys.  
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37 66 • A reliable local mobile data network ensured timely and effective study coordination,  
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39 67 data collection, and quality controls.  
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41 68 • The proposed diagnostic and treatment solutions presented specific challenges and were  
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43 69 less reliable than expected.  
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## 72 INTRODUCTION

73 Cervical cancer represents the most common cancer among females in Bhutan, with an age-  
74 standardised incidence rate of approximately 13 cases per 100,000 person years.<sup>1</sup> The country is  
75 strongly engaged in the prevention of cervical cancer. In the year 2000, the Ministry of Health  
76 launched a national cytology-based screening programme, and a Pap smear is currently  
77 recommended every three years to women aged 25–65 years.<sup>2</sup> In the year 2010, Bhutan was the  
78 first low/middle-income country (LMIC) to initiate a successful national vaccination programme  
79 against human papillomavirus (HPV) with >90% coverage in girls age 12–18 years.<sup>3</sup> Conversely,  
80 screening coverage is much lower and fairly heterogeneous across the country, ranging from  
81 20% to 60% of the target population in different provinces.<sup>4,5</sup> In rural areas, where approximately  
82 60% of the Bhutanese live,<sup>6</sup> cytology-based screening campaigns are occasionally conducted but  
83 coverage remains poor,<sup>4</sup> and follow-up and treatment of screening-positive women is  
84 challenging.

85 Organized screening programmes are demanding in terms of administrative, human, financial,  
86 and logistic resources. Pap smear-based programmes require frequent visits, trained staff, and  
87 strict quality control. In contrast, HPV-based screening allows for longer screening intervals,<sup>7,8</sup>  
88 self-sampling,<sup>9</sup> and automation of the diagnostic procedure. It is therefore an attractive option to  
89 improve the acceptability and cost-effectiveness of screening.<sup>10</sup>

90 In 2016, the Ministry of Health of Bhutan and the International Agency for Research on  
91 Cancer (IARC) implemented the “REACH-Bhutan” study to assess the feasibility, outcomes, and  
92 challenges of cervical cancer screening based on the *careHPV* test on self-collected samples  
93 among women 30–60 years of age in rural areas of the country. In the current report, we describe  
94 the study design, target population, recruitment and sample collection methods, key

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3 95 characteristics of study participants, and patterns of participation. Details on the performance of  
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5 96 *careHPV* testing and clinical management of *careHPV*-positive women will be reported in future  
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8 97 publications.  
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## 12 13 99 **MATERIAL AND METHODS**

### 14 15 100 Study population and recruitment

16  
17 101 Our study targeted women aged 30–60 years living in rural areas; recruitment and sample  
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20 102 collection took place from April to May 2016 in Basic Health Units (BHUs), the facilities that  
21  
22 103 provide primary health care to the Bhutanese population. The Bhutanese principal investigator  
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24 104 (UT) selected 15 BHUs that differed by accessibility, size, and ethnic composition of the served  
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27 105 population (Figure 1). Lists of household members in each village were obtained from the BHU  
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29 106 survey produced yearly for demographic purposes.

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31 107 Local health workers (HWs) familiar with community mobilization were instructed by  
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33  
34 108 the principal investigator in the specifics of self-sampling for cervical screening, and visited the  
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36 109 villages served by the selected BHUs to invite eligible women to come to the BHU to participate  
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39 110 in the study on specified dates. The benefits of cervical cancer screening and the purposes of the  
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41 111 study were explained to the women during public invitation sessions. All women from a given  
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43 112 village were invited to attend screening at the BHUs on the same date. Pregnant women, women  
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46 113 with mental disability, who had undergone hysterectomy or planned to leave the study area in the  
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48 114 next 6 months were not eligible.

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50 115 On the appointment date, two or three HWs and one of the two mobile study teams (one  
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53 116 for East and one for West Bhutan, each composed of two nurses and supervised by a  
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55 117 gynaecologist) provided additional information on the study, collected an informed consent  
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3 118 form, and administered a short electronic questionnaire on the BHU's premises. The entire  
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6 119 process required less than 20 minutes and certain BHUs were able to manage more than 100  
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8 120 women per day. Whenever possible, the recently introduced national citizenship identification  
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10 121 number (CID), which uniquely identifies Bhutanese citizens, and at least one mobile telephone  
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12 122 number were recorded for follow-up purposes.  
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#### 17 124 Sample collection, transportation, and laboratory analysis

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20 125 Each participant was asked to provide a self-collected cervico-vaginal sample using a  
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22 126 *careBrush*. They were instructed to insert the brush deep into the vagina and rotate it 3 to 5 times  
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24 127 before dipping it in a tube containing *careHPV* collection medium. The study team nurse  
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26 128 provided guidance to the participants on how to perform self-collection but did not attend the  
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28 129 self-collection procedure. Tubes were then stored in fridges until they were transported in cool  
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30 130 boxes to the central laboratory of Jigme Dorji Wangchuck National Referral Hospital  
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32 131 (JDWNRH) in Thimphu. Samples were stored at  $\sim 4^{\circ}\text{C}$  and an aliquot was tested using the  
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34 132 *careHPV* platform (Qiagen Corporation, Gaithersburg, MD, USA) according to the  
35  
36 133 manufacturer's instructions. The *careHPV* test is a validated signal-amplification, rapid batch  
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38 134 diagnostic test for the detection of DNA of 13 high risk (HR) HPV types (HPV16, 18, 31, 33, 35,  
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40 135 39, 45, 51, 52, 56, 58, 59, 68) and HPV66.<sup>11</sup> *careHPV* results were communicated by the central  
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42 136 laboratory as soon as possible to each BHU (after a median of 11 days; inter-quartile range: 9 to  
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44 137 33 days) to arrange follow-up of *careHPV*-positive women and of a random fraction of  
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46 138 *careHPV*-negative women, as a quality control measure.  
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#### 55 140 Data collection and statistical analyses

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3 141 All information on study participants and biological samples were collected and stored on  
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6 142 portable electronic devices. Whenever a mobile data network was accessible, the stored data  
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8 143 were uploaded to the IARC server and portable devices were synchronized with the most recent  
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10 144 version of the study database. The distribution of the target population in each BHU by age  
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12 145 group and by village of residence was obtained from the demographic survey conducted in year  
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14 146 2015. Travelling time was estimated from each village of residence to the corresponding BHU.  
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17 147 On account of the socio-geographic characteristics of the study areas, most women had to reach  
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19 148 the BHU on foot. We subdivided the travelling time into seven categories (i.e. <30 minutes, 30 to  
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21 149 59 minutes, 1 hour to 1 hour 59 minutes, 2 hours to 2 hours 59 minutes, 3 hours to 3 hours 59  
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23 150 minutes, 4 hours to 5 hours 59 minutes, and 6 or more hours), and fitted a mixed-effect logistic  
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25 151 model to data to assess the influence of travelling time on study participation, with BHUs as  
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27 152 clusters.

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31 153 Among participating women, we assessed prevalence ratios (PR) and corresponding 95%  
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33 154 confidence intervals (CI) for lack of previous cervical cancer screening and *careHPV* positivity  
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35 155 according to selected characteristics using binomial regression models with a log link and  
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37 156 adjustment for age group (30–39, 40–49, and  $\geq 50$  years) and BHU of recruitment, as appropriate.  
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39 157 For each variable of interest, missing or undisclosed (i.e. labelled as “prefer not to answer”)  
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41 158 information were treated as not informative and excluded from the analyses.  
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## 48 160 RESULTS

49  
50 161 Out of 15 BHUs included in “REACH-Bhutan”, 6 are located in West Bhutan and 9 in  
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52 162 East Bhutan (Figure 1). They serve a total of 3,648 women age 30–60 years (Figure 2). Overall  
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54 163 participation was 71% (95% CI: 69.5%–72.5%) and was similar in the West and the East. It  
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3 164 was, however, significantly heterogeneous by BHU (range: 31%–96%, I-square 99%,  $p < 0.001$ ),  
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5 165 and age group (81% in 30–39 year-old women but only 59% in  $\geq 50$  years). Participation steadily  
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7 166 decreased with the increase in travelling time from village to BHU being 90% (95% CI: 84%–  
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9 94%) for women living less than 30 minutes from the BHU but 62% (95% CI: 50%–73%)  
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11 167 among those 6 hours away or more (see appendix p1). The influence of travelling time strongly  
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13 168 increased with a woman's age: the drop in participation between 30 minutes and 6 hours was  
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15 169 from 93% (95% CI: 87%–96%) to 76% (95% CI: 64%–84%) among women 30–39 years old,  
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17 170 but from 86% (95% CI: 75%–92%) to 45% (95% CI: 30%–62%) among women  $\geq 50$  years  
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19 171 (Figure 3). The village of residence was not reported by 6 women or did not belong to the BHU  
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21 172 catchment area (7 women). These women did not contribute to the analysis reported in Figure 3.  
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25 174 A total 2,590 women accepted the invitation and came to a BHU (median age: 41 years;  
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27 175 inter-quartile range: 35 to 49 years). Ninety-nine percent belonged to 4 ethnic groups: Sarchop  
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29 176 (55%); Lhotsampa (27%); Ngalop (13%); and Khengpa (4%), each group predominating in at  
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31 177 least one BHU (Figure 1). All but two women provided a telephone number and 60% provided  
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33 178 their identity card number. Most women stated that self-sampling was easy to perform (96%) and  
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35 179 painless (90%). Macroscopic blood traces were observed in 3.5% of sample of non-menstruating  
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37 180 women (data not shown).  
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40 181 Fifty percent of participants reported having had previous screening (Figure 4A) and, among  
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42 182 them, 83% had had a Pap smear in the last 4 years (data not shown). The proportion of never-  
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44 183 screened women varied across individual BHUs (range: 2%–72%,  $I^2 = 99%$ ,  $P\text{-value} < 0.001$ ).  
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46 184 Table 1 shows the characteristics that were significantly associated with lack of screening, i.e.,  
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48 185 age group (PR for  $\geq 50$  vs. 30–39 years = 1.36; 95% CI: 1.26–1.47); region (PR for West vs.  
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50 186 East = 2.84; 95% CI: 2.05–3.95); travelling time from village to BHU (PR for  $\geq 6$  hours vs.  $< 1$   
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3 187 hour =1.53; 95% CI: 1.38–1.69); ethnicity (PR vs. Scharchop = 1.65; 95% CI: 1.52–1.80 for  
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5 188 Ngalop; 1.41; 95% CI: 1.29–1.53 for Lhotsampa; and 0.58; 95% CI: 0.41–0.81 for Khengpa);  
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8 189 educational level (PR for literate vs. illiterate =0.85; 95% CI: 0.73–0.99); occupation (PR for  
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10 190 shopkeepers/saleswoman/manual worker vs. farmer/housewives =0.56; 95% CI: 0.34–0.90);  
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12 191 marital status (PR for never married vs. married = 1.35; 95% CI: 1.07–1.71); and nulliparity (PR  
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14 192 for 0 vs.  $\geq 3$  = 1.25; 95% CI: 1.05–1.49. Lifetime number of sexual partners, age at first sexual  
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16 193 intercourse, and *careHPV* positivity were unrelated to screening history (Table 1).  
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20 194 Overall, 265 women (10%; 95% CI 9%–11%) were *careHPV*-positive with a significant  
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22 195 variation by BHU (range: 5%–19%,  $I^2 = 63%$ , P-value<0.001) (Figure 4B). Table 2 shows the  
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24 196 relationship between *careHPV* positivity and various women’s characteristics. Significant risk  
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26 197 factors for HPV positivity included region of Bhutan (PR for West vs. East =0.55; 95% CI:  
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28 198 0.30–1.00), marital status (PR for widow, separated or divorced vs. married=1.71; 95% CI: 1.21–  
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30 199 2.41), number of pregnancies (PR for 1–2 vs.  $\geq 3$  =1.49; 95% CI: 1.15–1.93), and lifetime  
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32 200 number of sexual partners (PR for  $\geq 3$  vs. 0–1=1.55; 95% CI: 1.05–2.27). *careHPV* positivity  
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34 201 was not significantly associated with age, ethnicity, educational level, occupation, age at first  
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36 202 sexual intercourse, and lack of previous screening (Table 2).  
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## 44 204 **DISCUSSION**

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46 205 The findings from “REACH-Bhutan” show that community-based cervical cancer  
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48 206 screening using self-collected samples and *careHPV* test is feasible in BHUs and can achieve  
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50 207 high-coverage in rural Bhutan. Our study, therefore, can be added to an increasing number of  
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52 208 evaluations of the implementation of *care-HPV* screening in under-served populations of Asia,  
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54 209 <sup>12-14</sup> Africa, <sup>15-17</sup> and Latin America. <sup>18 19</sup>  
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3 210 Seventy percent of women from rural communities responded favourably to the invitation  
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6 211 to come to their BHU to undergo HPV screening. In comparison, in Thimphu, the Bhutanese  
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8 212 capital, only 33% (95% CI: 29–37) of invited women of the same age group accepted to take part  
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10 213 in a study of clinician collected samples.<sup>5</sup> However, participation significantly decreased with  
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12 214 increasing age and travelling time between the village of residence and the BHU. The negative  
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14 215 effect of living far away from a BHU was especially strong among older women. Furthermore,  
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16 216 older age and large distance from BHUs were confirmed to be risk factors for lack of previous  
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18 217 screening among the women who participated in our present study (Table 1).  
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22 218 The large majority of study participants reported to be illiterate farmers or housewives,  
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24 219 currently married and sexually active. One-fifth reported two sexual partners or more, and 74%  
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26 220 three children or more. Among study participants, 50% had never been screened before,  
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28 221 confirming that rural areas are underserved compared to Thimphu, where 33% (95% CI: 30–36)  
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30 222 of 30–60 year-old study participants had never been screened.<sup>5</sup> Despite the remarkable socio-  
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32 223 demographic homogeneity of the rural communities included, participation in “REACH-Bhutan”  
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34 224 and history of previous screening among participating women were significantly different among  
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36 225 BHUs pointing to different levels of success in application of the national guidelines.  
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41 226 The varying degree of participation in our current study and of previous screening across  
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43 227 BHUs may be also related to differences in ethnic composition. Indeed, lack of previous  
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45 228 screening was significantly more frequent among women who belonged to the Lhotsampa  
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47 229 (mostly Hindus) and Ngalop (mostly Buddhist) ethnic groups. It is, however, unclear whether  
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49 230 Lhotsampa and Ngalop were more reluctant to be screened or lived in areas where BHUs were  
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51 231 less committed to screening. For example, in the large BHU of Bara, at the western border with  
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53 232 India, there was a suggestion that a historical absence of female HWs had had a negative impact  
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3 233 on cervical screening attendance. The few literate women and those who were shopkeepers or  
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5 234 manual workers reported more screening attendance.  
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8 235 Ten percent of women were *careHPV*-positive, i.e. a percentage only slightly lower than  
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10 236 that found in Thimphu in the same age group, i.e. 14.1% (95% CI: 12.0–16.4).<sup>20</sup> Lifetime  
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12 237 number of sexual partners, being widowed, separated or divorced, and having had 1 or 2 children  
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14 238 (as compared to 3) were significantly associated with HPV positivity as reported in previous  
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16 239 IARC HPV surveys.<sup>21 22</sup> Women in West Bhutan were less likely to be HPV positive than their  
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18 240 counterparts in the east of the country and this finding is likely to reflect differences in lifestyle  
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20 241 sexual habits across rural communities or ethnic groups. In fact, the percentage of women who  
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22 242 reported two or more sexual partners was 15% in the West versus 26% in the East.  
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27 243 The main strengths of the present study are the inclusion of a large number of women  
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29 244 from many rural villages and the relatively high and accurately estimated participation of invited  
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31 245 30–60 year-old women. We developed an mHealth platform and relied on the local mobile data  
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33 246 network to ensure a timely and effective coordination of BHU HWs and mobile study teams  
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35 247 across Bhutan, and to manage data collection, transmission, and real-time quality controls.<sup>23 24</sup>  
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37 248 Furthermore, virtually all study participants had access to at least one mobile phone, greatly  
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39 249 simplifying their recall for follow-up visits.  
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43 250 However, study implementation was also characterised by logistic and technological  
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45 251 challenges. For example, although the central laboratory in Thimphu was able to deliver  
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47 252 *careHPV* results to each BHU in a median of 11 days after screening, the *careHPV* platform  
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49 253 turned out to be less reliable than expected and, even after completion of the initial training  
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51 254 period, there still continued to be substantial wastage due to invalid *careHPV* runs. In addition,  
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53 255 the original plan of rapidly recalling women and offering them colposcopy triage and, if  
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3 256 necessary, cryotherapy in each BHU was hindered by difficulties in transport and/or malfunction  
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6 257 of cryotherapy equipment.

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8 258 At end March 2017, 248 (94%) *care*HPV positive women had had a follow up visit and  
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10 259 217 had undergone either cryotherapy (n=88) or loop electrosurgical excision procedure (LEEP,  
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12 260 n=129). Histological ascertainment of cervical specimens from these women (as well as from a  
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15 261 subset of *care*-HPV negative women) is still ongoing, and clinical outcomes will be the subject  
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17 262 of a future publication.

## 19 263 **CONCLUSION**

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22 264 The “REACH-Bhutan” study shows both the readiness of the Bhutanese Health System,  
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24 265 and the willingness and resilience of Bhutanese women, to comply with cervical cancer  
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27 266 screening algorithms based on self-collection for HPV testing. It also highlights, however, the  
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29 267 need to find new solutions to specific challenges, such as bringing self-collection even closer to  
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31 268 women, especially older ones living in the remotest areas, possibly in coordination with the  
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33 269 decentralized offer of other primary health care activities, e.g., child vaccination, which are  
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36 270 regularly brought from BHUs to villages.

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12  
13 279 **Contributors**  
14

15 280 IB, ST, SF, GC, and UT conceived and designed the study. IB, SF, GC, and UT drafted  
16  
17 281 the manuscript. ST, TC, FL, VT, and MP critically revised the manuscript. All authors  
18  
19 282 substantially contributed to the acquisition, analysis, and interpretation of data and approved the  
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21 283 final manuscript.  
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23

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35  
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39 290 **Competing interests**  
40

41 291 None declared.  
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44 292 **Ethics approval**  
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46 293 The present study had the approval of both the Research Ethical Board of the Bhutan  
47  
48 294 Ministry of Health and the IARC Ethics Committee.  
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51 295 **Provenance and peer review**  
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53 296 Not commissioned; externally peer reviewed.  
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56 297 **Data sharing statement**  
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298 No additional data are available.

For peer review only

299 **References**

- 300 1. Ervik M, Lam F, Ferlay J, et al. Cancer Today Lyon, France: International Agency for  
301 Research on Cancer. 2016 [Available from: <http://gco.iarc.fr/today> accessed 11  
302 November 2016].
- 303 2. Dhendup T, Tshering P. Cervical cancer knowledge and screening behaviors among female  
304 university graduates of year 2012 attending national graduate orientation program,  
305 Bhutan. *BMC Womens Health* 2014;14(1):44.
- 306 3. Dorji T, Tshomo U, Phuntsho S, et al. Introduction of a National HPV vaccination program  
307 into Bhutan. *Vaccine* 2015;33(31):3726-30. doi: 10.1016/j.vaccine.2015.05.078
- 308 4. Ministry of Health. National Health Survey. Thimphu, Bhutan: Ministry of Health 2012.
- 309 5. Baussano I, Tshomo U, Clifford GM, et al. Cervical cancer screening program in Thimphu,  
310 Bhutan: population coverage and characteristics associated with screening attendance.  
311 *Bmc Womens Health* 2014;14:147. doi: 10.1186/s12905-014-0147-0
- 312 6. The World Bank. Rural population (% of total population). [Available from:  
313 <http://data.worldbank.org/indicator/SP.RUR.TOTL.ZS?locations=BT> accessed 11  
314 January 2017].
- 315 7. Arbyn M, Anttila A, Jordan J, et al. European Guidelines for Quality Assurance in Cervical  
316 Cancer Screening. Second edition--summary document. *Ann Oncol* 2010;21(3):448-58.  
317 doi: 10.1093/annonc/mdp471
- 318 8. Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of  
319 invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet*  
320 2014;383(9916):524-32. doi: 10.1016/S0140-6736(13)62218-7

- 1  
2  
3 321 9. Arrossi S, Thouyaret L, Herrero R, et al. Effect of self-collection of HPV DNA offered by  
4  
5 322 community health workers at home visits on uptake of screening for cervical cancer (the  
6  
7 323 EMA study): a population-based cluster-randomised trial. *Lancet Glob Health*  
8  
9 324 2015;3(2):e85-94. doi: 10.1016/S2214-109X(14)70354-7  
10  
11  
12 325 10. Tsu V, Jeronimo J. Saving the World's Women from Cervical Cancer. *N Engl J Med*  
13  
14 326 2016;374(26):2509-11. doi: 10.1056/NEJMp1604113  
15  
16  
17 327 11. Qiao YL, Sellors JW, Eder PS, et al. A new HPV-DNA test for cervical-cancer screening in  
18  
19 328 developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet*  
20  
21 329 *Oncol* 2008;9(10):929-36. doi: 10.1016/S1470-2045(08)70210-9  
22  
23  
24 330 12. Qiao YL, Sellors JW, Eder PS, et al. A new HPV-DNA test for cervical-cancer screening in  
25  
26 331 developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet*  
27  
28 332 *Oncol* 2008;9(10):929-36.  
29  
30  
31 333 13. Tuerxun G, Yukejaier A, Lu L, et al. Evaluation of careHPV, Cervista Human  
32  
33 334 Papillomavirus, and Hybrid Capture 2 Methods in Diagnosing Cervical Intraepithelial  
34  
35 335 Neoplasia Grade 2+ in Xinjiang Uyghur Women. *Oncologist* 2016;21(7):825-31. doi:  
36  
37 336 10.1634/theoncologist.2015-0447 [published Online First: 2016/06/19]  
38  
39  
40 337 14. Labani S, Asthana S. Age-specific performance of careHPV versus Papanicolaou and visual  
41  
42 338 inspection of cervix with acetic acid testing in a primary cervical cancer screening. *J*  
43  
44 339 *Epidemiol Community Health* 2016;70(1):72-7. doi: 10.1136/jech-2015-205851  
45  
46 340 [published Online First: 2015/08/08]  
47  
48  
49 341 15. Obiri-Yeboah D, Adu-Sarkodie Y, Djigma F, et al. Options in human papillomavirus (HPV)  
50  
51 342 detection for cervical cancer screening: comparison between full genotyping and a rapid  
52  
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3 343 qualitative HPV-DNA assay in Ghana. *Gynecologic oncology research and practice*  
4  
5 344 2017;4:5. doi: 10.1186/s40661-017-0041-1 [published Online First: 2017/03/09]  
6  
7  
8 345 16. Segondy M, Kelly H, Magooa MP, et al. Performance of careHPV for detecting high-grade  
9  
10 346 cervical intraepithelial neoplasia among women living with HIV-1 in Burkina Faso and  
11  
12 347 South Africa: HARP study. *Br J Cancer* 2016;115(4):425-30. doi: 10.1038/bjc.2016.207  
13  
14 348 [published Online First: 2016/07/20]  
15  
16  
17 349 17. Bansil P, Lim J, Byamugisha J, et al. Performance of Cervical Cancer Screening Techniques  
18  
19 350 in HIV-Infected Women in Uganda. *J Low Genit Tract Dis* 2015;19(3):215-9. doi:  
20  
21 351 10.1097/lgt.0000000000000090 [published Online First: 2015/01/01]  
22  
23  
24 352 18. Lorenzi AT, Fregnani JH, Possati-Resende JC, et al. Can the careHPV test performed in  
25  
26 353 mobile units replace cytology for screening in rural and remote areas? *Cancer Cytopathol*  
27  
28 354 2016;124(8):581-8. doi: 10.1002/cncy.21718 [published Online First: 2016/04/14]  
29  
30  
31 355 19. Maza M, Alfaro K, Garai J, et al. Cervical cancer prevention in El Salvador (CAPE)-An  
32  
33 356 HPV testing-based demonstration project: Changing the secondary prevention paradigm  
34  
35 357 in a lower middle-income country. *Gynecologic oncology reports* 2017;20:58-61. doi:  
36  
37 358 10.1016/j.gore.2017.02.011 [published Online First: 2017/03/25]  
38  
39  
40 359 20. Tshomo U, Franceschi S, Dorji D, et al. Human papillomavirus infection in Bhutan at the  
41  
42 360 moment of implementation of a national HPV vaccination programme. *BMC Infect Dis*  
43  
44 361 2014;14:408. doi: 10.1186/1471-2334-14-408  
45  
46  
47  
48 362 21. Vaccarella S, Franceschi S, Herrero R, et al. Sexual behavior, condom use, and human  
49  
50 363 papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys.  
51  
52 364 *Cancer Epidemiol Biomarkers Prev* 2006;15(2):326-33. doi: 10.1158/1055-9965.EPI-05-  
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3 366 22. Vaccarella S, Herrero R, Dai M, et al. Reproductive factors, oral contraceptive use, and  
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5  
6 367 human papillomavirus infection: pooled analysis of the IARC HPV prevalence surveys.  
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8 368 *Cancer Epidemiol Biomarkers Prev* 2006;15(11):2148-53. doi: 10.1158/1055-9965.EPI-  
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10 369 06-0556  
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12 370 23. Hall CS, Fottrell E, Wilkinson S, et al. Assessing the impact of mHealth interventions in low-  
13  
14 371 and middle-income countries--what has been shown to work? *Glob Health Action*  
15  
16 372 2014;7:25606. doi: 10.3402/gha.v7.25606  
17  
18 373 24. Howitt P, Darzi A, Yang GZ, et al. Technologies for global health. *Lancet*  
19  
20 374 2012;380(9840):507-35. doi: 10.1016/S0140-6736(12)61127-1  
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377 **Table 1: Prevalence ratios (PR) for lack of previous cervical cancer screening and**  
 378 **corresponding 95% confidence intervals (CI) according to selected characteristics, Bhutan,**  
 379 **2016**

Characteristic	N tested	Never screened N (%)	Adjusted PR*	95% CI
<b>Age (years)</b>				
30–39	1139	497 (43.6)	1	–
40–49	818	407 (49.8)	1.14	1.05–1.24
≥50	633	383 (60.5)	1.36	1.26–1.47
$\chi^2_1$ for trend			<i>p</i> <0.001	
<b>Region</b>				
East	1500	625 (41.7)	1	–
West	1090	662 (60.7)	2.84	2.05–3.95
<b>Travel time from village to BHU (hours)<sup>†</sup></b>				
<1	656	285 (43.5)	1	–
1–5	1287	576 (44.8)	1.01	0.91–1.12
Missing	6	4 (66.7)	–	–
≥6–	641	422 (65.8)	1.53	1.38–1.69
$\chi^2_1$ for trend			<i>p</i> <0.001	
<b>Ethnicity<sup>†</sup></b>				
Scharchop	1435	615 (42.9)	1	–
Ngalop	340	236 (69.4)	1.65	1.52–1.80
Lhotsampa	686	401 (58.5)	1.41	1.29–1.53
Khengpa	113	26 (23.0)	0.58	0.41–0.81
Other	16	9 (56.3)	1.49	0.97–2.31
<b>Education level</b>				
Illiterate	2372	1191 (50.2)	1	–
Literate	218	96 (44.0)	0.85	0.73–0.99
<b>Current occupation</b>				
Farmer/ housewife	2488	1254 (50.4)	1	–
Shopkeeper/saleswoman/manual worker	53	12 (22.6)	0.56	0.34–0.90
Clerical staff/teacher/health worker/nun	49	21 (42.9)	0.97	0.72–1.31
<b>Marital status<sup>†</sup></b>				
Married/living as married	2390	1175 (49.2)	1	–

Never married	21	16 (76.2)	1.35	1.07–1.71
Widow/separated/divorced	179	96 (53.6)	1.05	0.92–1.21
<b>Number of pregnancies<sup>†</sup></b>				
0	67	43 (64.2)	1.25	1.05–1.49
1–2	604	285 (47.2)	1.03	0.94–1.14
≥3	1919	959 (50.0)	1	–
$\chi^2_1$ for trend				<i>p</i> =0.057
<b>Lifetime number of sexual partners</b>				
0–1	2020	983 (48.7)	1	–
2	341	166 (48.7)	0.97	0.88–1.08
≥3	214	126 (58.9)	0.98	0.88–1.09
Prefer not to answer	15	12 (80.0)	–	–
$\chi^2_1$ for trend				<i>p</i> =0.601
<b>Age at first sexual intercourse (years)<sup>‡</sup></b>				
9–14	245	124 (50.6)	1	–
15–16	515	235 (45.6)	0.93	0.81–1.06
17–19	968	452 (46.7)	1.00	0.89–1.12
≥20	707	365 (51.6)	1.02	0.91–1.15
Prefer not to answer / unknown	143	101 (70.6)	–	–
$\chi^2_1$ for trend				<i>p</i> =0.151
<b>HPV infection</b>				
Negative	2325	1168 (50.2)	1	–
Positive	265	119 (44.9)	1.01	0.91–1.13

380 CI=confidence interval; HPV=human papillomavirus; PR=prevalence ratio. \*Adjusted for age (3 classes: 30–39; 40–49; 50+) and  
 381 Basic Health Unit as appropriate. †Adjusted for age only – when adjusted for BHU, model does not converge. ‡Among sexually  
 382 active women.

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385 **Table 2: Prevalence ratios (PR) for high-risk human papillomavirus (HPV) positivity and**  
 386 **corresponding 95% confidence intervals (CI) according to selected characteristics, Bhutan,**  
 387 **2016**

Characteristic	N tested	care-HPV positive N (%)	Adjusted PR*	95% CI
<b>Age (years)</b>				
30–39	1139	129 (11.3)	1	–
40–49	818	76 (9.3)	0.80	0.62–1.05
≥50	633	60 (9.5)	0.79	0.59–1.05
$\chi^2_1$ for trend			<i>p=0.073</i>	
<b>Region</b>				
East	1500	173 (11.5)	1	–
West	1090	92 (8.4)	0.55	0.30–1.00
<b>Ethnicity</b>				
Scharchop	1435	164 (11.4)	1	–
Ngalop	340	28 (8.2)	0.68	0.31–1.49
Lhotsampa	686	58 (8.5)	0.67	0.33–1.38
Khengpa	113	15 (13.3)	1.80	0.31–10.5
Other	16	0 (0)	–	–
<b>Education level</b>				
Illiterate	2372	238 (10.0)	1	–
Literate	218	27 (12.4)	1.33	0.90–1.95
<b>Current occupation</b>				
Farmer/ housewife	2488	253 (10.2)	1	–
Shopkeeper/saleswoman/manual worker	53	3 (5.7)	0.56	0.18–1.68
Clerical staff/teacher/health worker/nun	49	9 (18.4)	1.65	0.90–3.01
<b>Marital status</b>				
Married/living as married	2390	232 (9.7)	1	–
Never married	21	3 (14.3)	1.53	0.54–4.38
Widow/separated/divorced	179	30 (16.8)	1.71	1.21–2.41
<b>Number of pregnancies</b>				
0	67	8 (11.9)	1.29	0.66–2.49
1–2	604	83 (13.7)	1.49	1.15–1.93

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3	≥3	1919	174 (9.1)	1	–
4	$\chi^2_1$ for trend			$p=0.007$	
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7	<b>Lifetime number of sexual partners</b>				
8	0–1	2020	198 (9.8)	1	–
9	2	341	36 (10.6)	1.20	0.85–1.69
10	≥3	214	31 (14.5)	1.55	1.05–2.27
11	Prefer not to answer	15	0 (0.0)	–	–
12	$\chi^2_1$ for trend			$p=0.022$	
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16	<b>Age at first sexual intercourse (years)†</b>				
17	9–14	245	21 (8.6)	1	–
18	15–16	515	48 (9.3)	1.05	0.64–1.71
19	17–19	968	109 (11.3)	1.20	0.76–1.89
20	≥20	707	72 (10.2)	1.11	0.69–1.79
21	Prefer not to answer / unknown	143	14 (9.8)	–	–
22	$\chi^2_1$ for trend			$p=0.576$	
23					
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26	<b>History of PAP smear (years)</b>				
27	Ever	1303	146 (11.2)	1	–
28	Never	1287	119 (9.3)	1.06	0.81–1.39
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388 CI=confidence interval; HPV=human papillomavirus; PR=prevalence ratio.\*Adjusted for age (3 classes: 30–39; 40–49; 50+) and  
 389 Basic Health Unit as appropriate. †Among sexually active women.

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3 391 **Figure Legends**  
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8 393 Figure 1: Map of Bhutan with study sites and predominant ethnic groups.\*  
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10 394 \*The size of each dot is proportional to the size of the target population of each centre.  
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15 396 Figure 2: Participation (%) and corresponding 95% confidence intervals by Basic Health Unit,  
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17 397 region, and age group, Bhutan, 2016.  
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21 399 Figure 3: Effect of travel time (on foot) on participation in REACH Bhutan, by age group,  
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23 400 Bhutan, 2016.  
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27 402 Figure 4: Percent of A) lack of previous cervical cancer screening; and B) *care*-HPV positivity  
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29 403 by Basic Health Unit and overall in rural areas and in Thimphu, Bhutan, 2016.  
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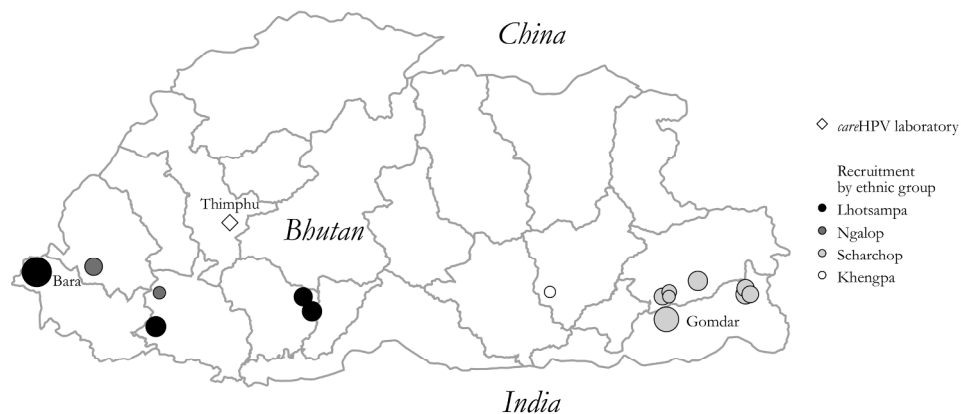


Figure 1: Map of Bhutan with study sites and predominant ethnic groups.\*  
The size of each dot is proportional to the size of the target population of each centre.

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Review only



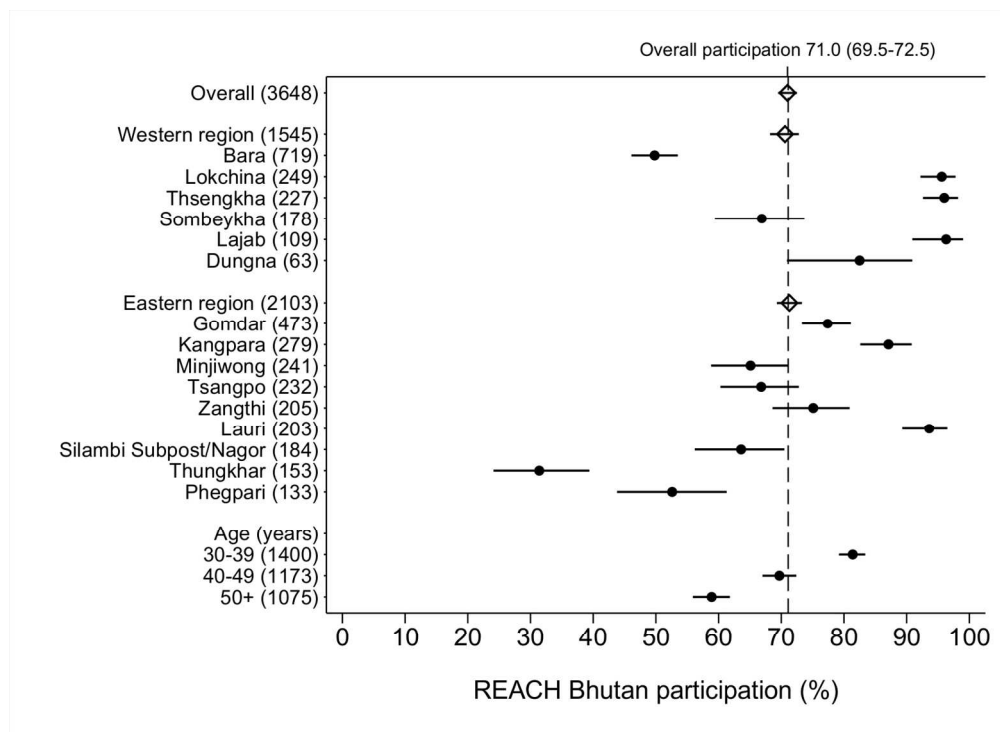


Figure 2: Participation (%) and corresponding 95% confidence intervals by Basic Health Unit, region, and age group, Bhutan, 2016.

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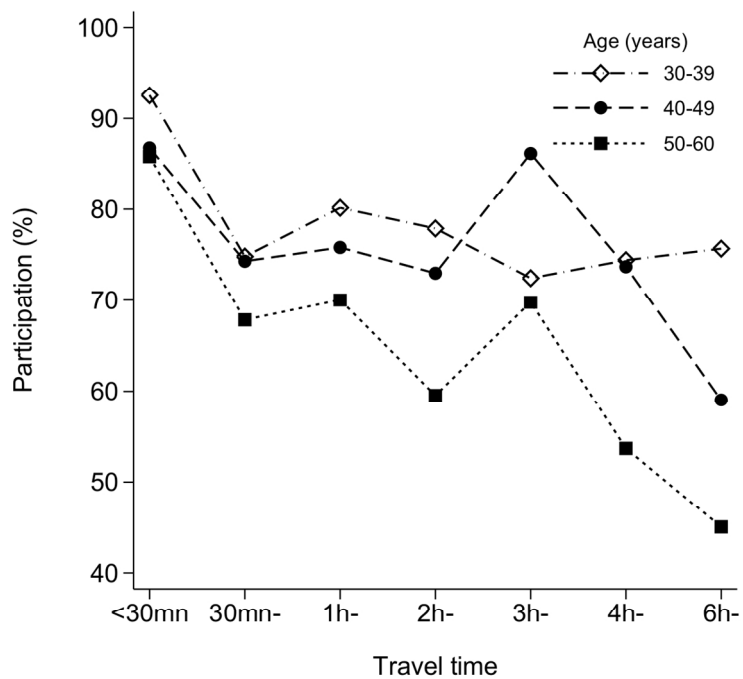


Figure 3: Effect of travel time (on foot) on participation in REACH Bhutan, by age group, Bhutan, 2016.

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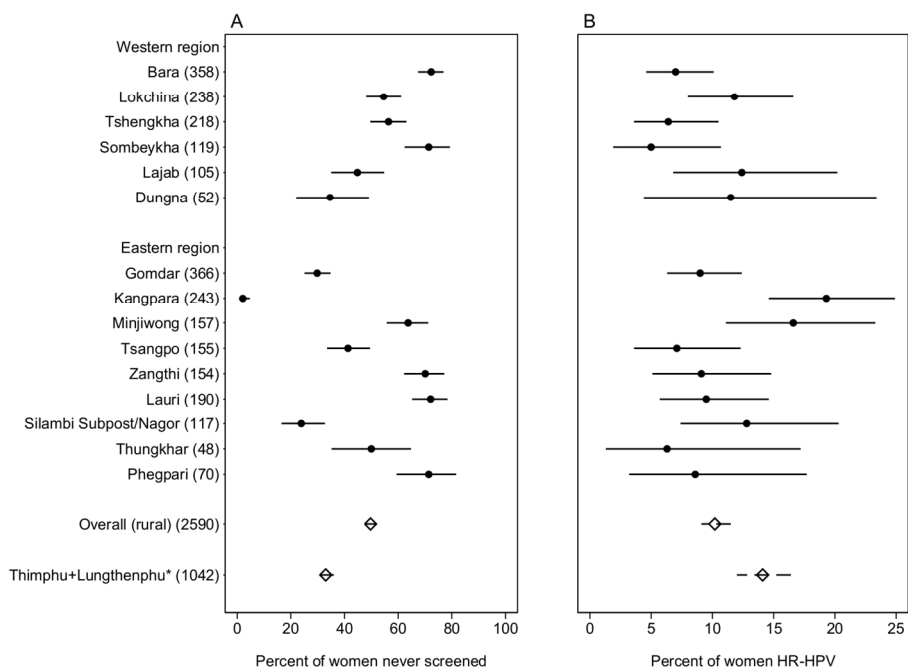
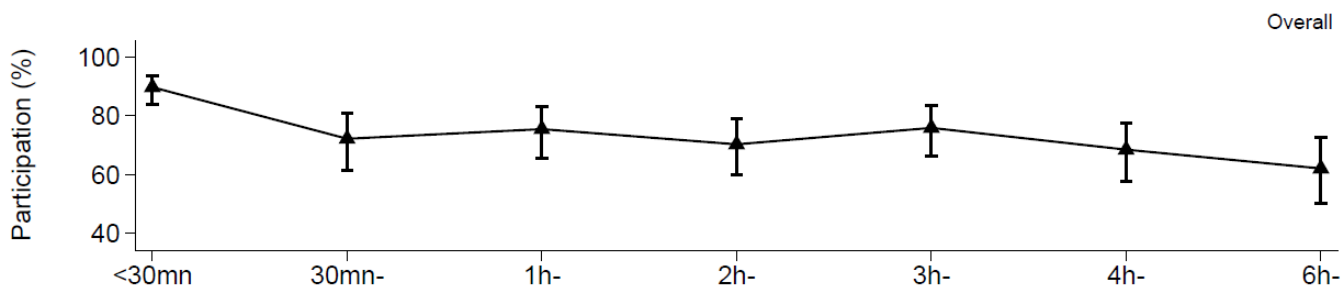


Figure 4: Percent of A) lack of previous cervical cancer screening; and B) care-HPV positivity by Basic Health Unit and overall in rural areas and in Thimphu, Bhutan, 2016.\*women aged 30-60 years in Tshomo et al 2014.

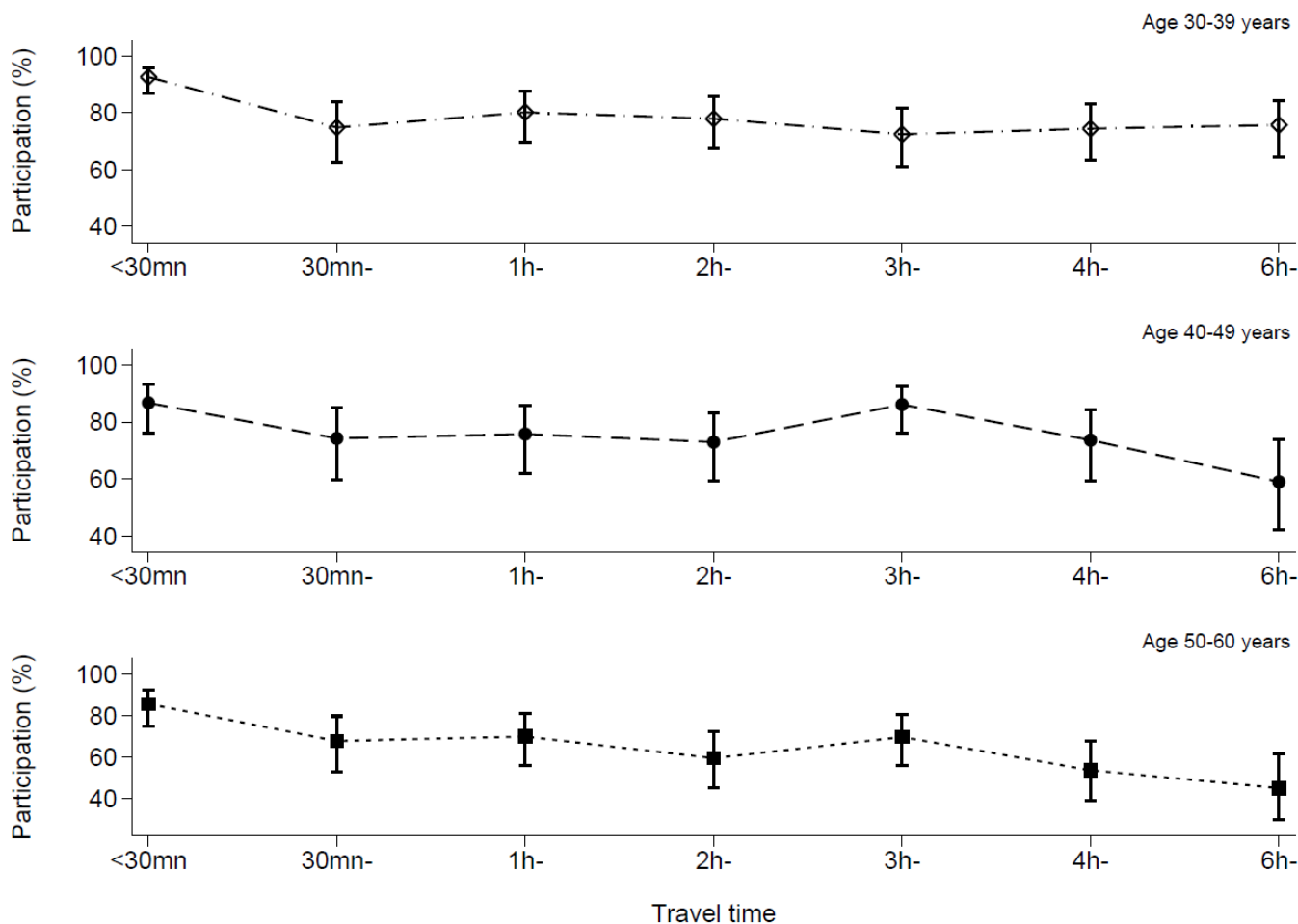
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Appendix Figure 1: Effect of travel time on participation (%) in REACH Bhutan, A) overall, B) by age group with 95% confidence interval, Bhutan, 2016

A



B



STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1/3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	8
		(d) If applicable, describe analytical methods taking account of sampling strategy	7
		(e) Describe any sensitivity analyses	NA
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Fig 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9; tables 1 & 2
		(b) Indicate number of participants with missing data for each variable of interest	9, tables 1 & 2
Outcome data	15*	Report numbers of outcome events or summary measures	9, Figure 2,4 and Tables
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted	9

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 1 & 2
		(b) Report category boundaries when continuous variables were categorized	Tables 1 & 2
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Figure 3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8, Figure 3
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).