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The cost-effectiveness of human papillomavirus self-collection among cervical cancer screening non-attenders in El Salvador

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ABSTRACT

Cervical cancer screening with human papillomavirus (HPV) DNA testing has been incorporated into El Salvador's national guidelines. The feasibility of home-based HPV self-collection among women who do not attend screening at the clinic (i.e., non-attenders) has been demonstrated, but cost-effectiveness has not been evaluated. Using cost and compliance data from El Salvador, we informed a mathematical microsimulation model of HPV infection and cervical carcinogenesis to conduct a cost-effectiveness analysis from the societal perspective. We estimated the reduction in cervical cancer risk, lifetime cost per woman (2017 US$), life expectancy, and incremental cost-effectiveness ratio (ICER, 2017 US$ per year of life saved [YLS]) of a program with home-based self-collection of HPV (facilitated by health promoters) for the 18% of women reluctant to screen at the clinic. The model was calibrated to epidemiologic data from El Salvador. We evaluated health and economic outcomes of the self-collection intervention for women aged 30 to 59 years, alone and in concert with clinic-based HPV provider-collection. Home-based self-collection of HPV was projected to reduce population cervical cancer risk by 14% and cost $1210 per YLS compared to no screening. An integrated program reaching 99% coverage with both provider- and home-based self-collection of HPV reduced cancer risk by 74% (compared to no screening), and cost $1210 per YLS compared to provider-collection alone. Self-collection facilitated by health promoters is a cost-effective strategy for increasing screening uptake in El Salvador.

1. Introduction

More than 80% of cervical cancer cases occur in low- and middle-income countries (LMIC), where access to primary and secondary prevention opportunities is limited. The World Health Organization (WHO) recommends that all countries introduce prophylactic vaccination against human papillomavirus, a necessary cause of cervical cancer, with one of the highly efficacious bivalent, quadrivalent, or nonavalent HPV vaccines (*Wkly Epidemiol. Rec.*, 2017), but vaccine costs and the logistical difficulties of reaching adolescent girls with two doses of the vaccine have made rapid scale-up challenging (Bruni et al., 2016). Meanwhile, for women past the target age for vaccination and those who have already been exposed to oncogenic HPV types, secondary prevention involving screening for precancerous lesions remains the only way to avert cervical cancer. Even one-time screening with HPV testing-based screening may reduce cervical cancer incidence and mortality rates by half (Sankaranarayanan et al., 2009). The WHO recommends HPV testing-based screening if resources are available (WHO, 2013), but few LMIC have begun to roll out national HPV testing-based screening programs. Organized screening efforts in LMIC have been hampered by the high cost of the HPV test; women's reluctance to receive pelvic exams; economic barriers to clinic

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attendance; and the current need for multiple contacts with the health system for screening and, if HPV-positive, subsequent treatment.

In El Salvador, where the age-standardized incidence rate of cervical cancer is 18.5 per 100,000 women (Bray et al., 2018), HPV DNA testing was introduced into the public health care system through a phased demonstration project in the Paracentral region beginning in 2012. During Phases 1 and 2 of the Cervical Cancer Prevention in El Salvador (CAPE) demonstration project, 10,050 women were screened to examine the feasibility, effectiveness, and cost-effectiveness of two different management algorithms for HPV-positive women (referral to colposcopy versus treatment with cryotherapy for eligible women) (Cremer et al., 2017). The Ministry of Health (MINSAL) incorporated the more effective and cost-effective HPV screen-and-treat algorithm (i.e., cryotherapy for eligible women) into national screening guidelines in 2015, and aims to scale HPV testing nationally as resources permit (Maza et al., 2017).

While participation in the CAPE project was high among women approached for the study (81%), approximately 12% of women who attended a Phase 1 informational session and were part of a screening adherence study (n = 409) did not attend subsequent screening appointments at their corresponding clinic. Factors associated with non-adherence included greater number of lifetime sexual partners and longer time since last cervical cancer screening (Alfaro et al., 2015). The CAPE project anticipated the need to reach women who did not schedule or attend their screening, and assessed the acceptability of HPV self-collection in a sub-sample of participants who were offered both provider- and self-collection of HPV at the clinic appointment (n = 518). Women viewed self-collection as equally or more preferred than provider-collection, due to greater privacy and less discomfort (Rosenbaum et al., 2014). In a subsequent study among women reluctant to screen at the clinic in the Paracentral region (n = 1869), of whom nearly 40% had not been screened within the past five years, 99% of study participants accepted self-collection when visited at home by a health promoter (Maza et al., 2018).

Studies in other low-resource settings have found that HPV self-collection is feasible, acceptable, and effective (Arrossi et al., 2015; Lazcano-Ponce et al., 2011; Moses et al., 2015), and may help improve screening uptake. Our objective was to estimate the cost-effectiveness of a home-based HPV self-collection program for screening non-attenders, by itself and in the context of an organized HPV testing-based screening program also offering clinic-based screening.

2. Methods

2.1. Modeling approach

We used a previously developed individual-based Monte Carlo simulation model of the natural history of HPV infection and cervical carcinogenesis to project the lifetime health and economic outcomes associated with an HPV self-collection program for women reluctant to screen in El Salvador (Campos et al., 2014; Campos et al., 2015a). The model was calibrated to epidemiologic data on HPV and cervical cancer burden in El Salvador. Model outcomes included lifetime risk of cervical cancer, total lifetime costs per woman (in 2017 US $), and life expectancy. We calculated incremental cost-effectiveness ratios (ICERs)—the additional cost of an intervention divided by its additional health benefit, relative to the next most costly strategy after eliminating strategies that are either more costly and less effective, or have higher ICERs than more effective strategies— in order to express cost-effectiveness results. While the selection of a willingness-to-pay threshold

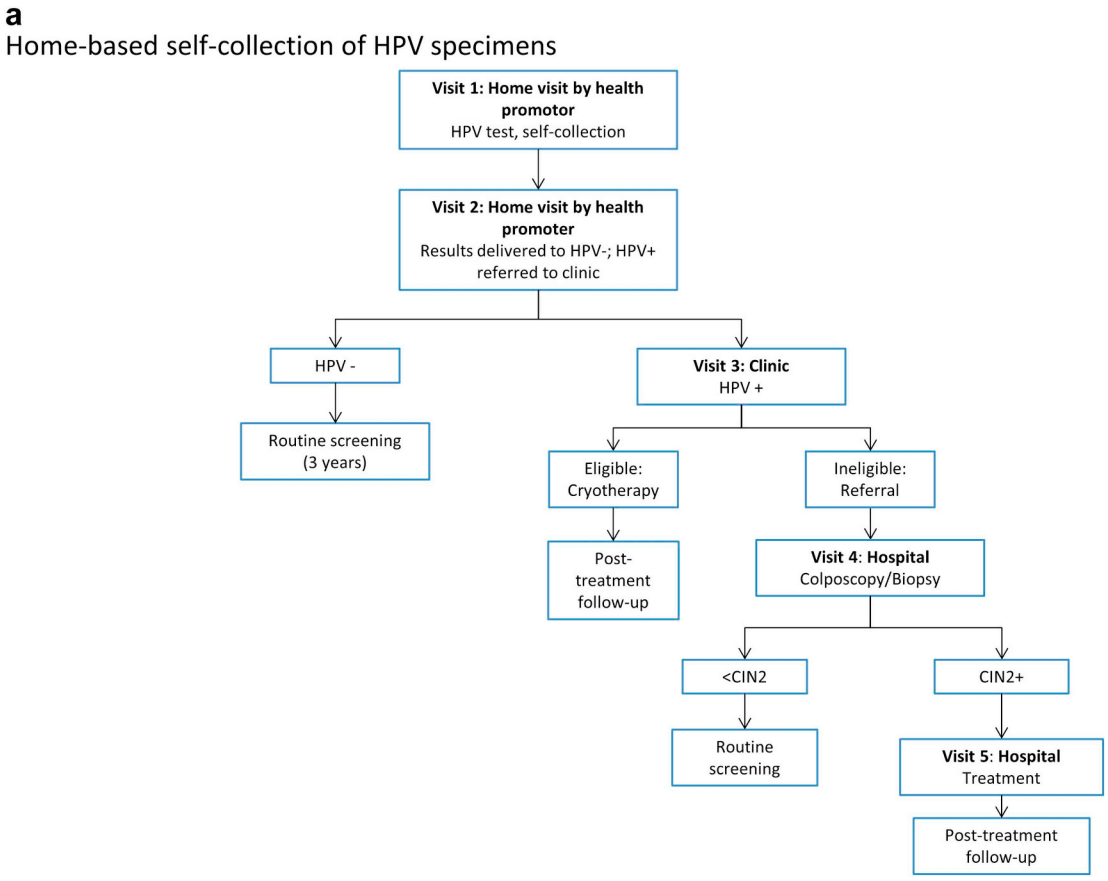

Fig. 1. Pathways of health care delivery: Home-based HPV self-collection vs. clinic-based provider-collection of HPV specimens. The diagrams indicate the flow of screening-eligible women through each point of contact in a screening episode for a) home-based HPV self-collection every 3 years for women reluctant to screen and b) clinic-based HPV provider-collection.

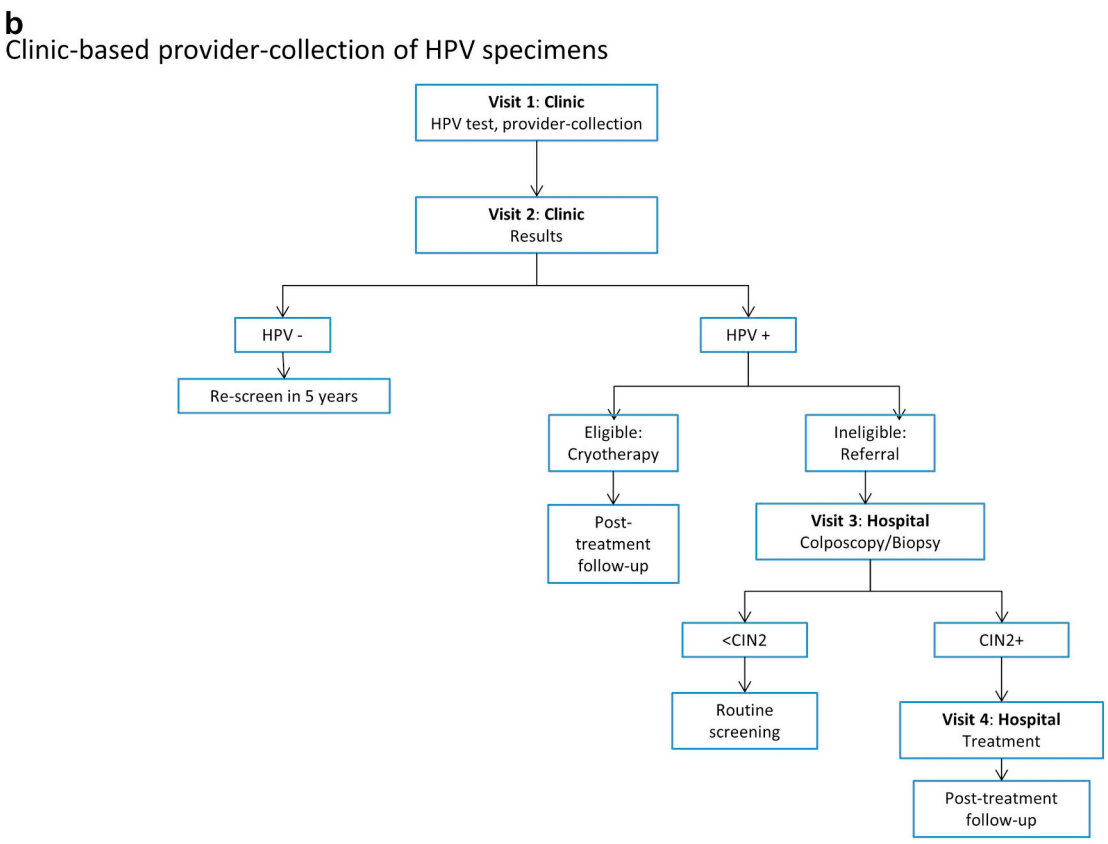

Fig. 1. (*continued*)

for the determination of whether an intervention is cost-effective remains controversial and setting-specific, we considered two different benchmarks for cost-effectiveness: 1) an ICER less than El Salvador's per capita GDP (2017 US$3890); and 2) an ICER less than 50% of El Salvador's per capita GDP (2017 US$1945) (WHO, 2001; *World Development Indicators*, 2018; Woods et al., 2016). In accordance with guidelines for cost-effectiveness analysis, we adopted a modified societal perspective (including direct medical costs and women's time and transportation costs, which are substantial in El Salvador and other low-resource settings (Goldie et al., 2005; Campos et al., 2015b)) and discounted future costs and life-years at a rate of 3% per year to account for time preferences (Jamison et al., 2006; Tan-Torres Edejer et al., 2003).

As described previously, a cohort of individual girls enters the simulation model at age 9 years, prior to sexual initiation. Each month, members of the cohort transition between mutually exclusive health states (including type-specific HPV infection, histologic grades of precancer [cervical intraepithelial neoplasia grade 2 or 3], and stage of cancer) until death from all-cause mortality or cervical cancer after its onset. Monthly transition probabilities may vary by age, HPV type, duration of infection or lesion status, and prior HPV infection. The model tracks the underlying natural history of disease (i.e., a woman's true health state), clinical events, and economic outcomes over the lifetime of each individual woman in the cohort. Cost and health outcomes are then aggregated over the cohort for analysis (Campos et al., 2014; Campos et al., 2015a).

We have described the derivation of model parameters and calibration process elsewhere (Campos et al., 2014; Campos et al., 2015a). Baseline transition probabilities were estimated from longitudinal data on age- and type-specific HPV incidence in a Colombian cohort, as well as time- and type-dependent rates of HPV clearance and progression to precancer from the placebo arm of the Costa Rica Vaccine Trial (Munoz et al., 2004; Sankaranarayanan et al., 2010; Rodriguez et al., 2010; (SEER) Program, 2011). The calibration process was necessary to reflect 1) the heterogeneity in HPV incidence and naturally acquired immunity following initial infection, which may vary between settings as a result of differences in sexual behavior and immune status; and 2) uncertainty in progression and regression of precancer due to the fact that these transitions are often unobservable. To calibrate the model, we set plausible ranges around the baseline transition probabilities. Repeated model simulations were performed in the absence of any intervention (i.e., natural history), selecting a single random value from the plausible range for each uncertain parameter to create a unique natural history input parameter set. We then computed a goodness-of-fit score by summing the log-likelihood of model-projected outcomes associated with each unique parameter set to determine the quality of fit to the epidemiologic data (i.e., calibration targets). Calibration targets for the El Salvador model used in this analysis included the age-specific prevalence of oncogenic HPV among women aged 30 to 49 years from Phase 2 of the CAPE project (Cremer et al., 2017); the prevalence of HPV16 and HPV18 in cervical cancer in South and Central America (Guan et al., 2012); and the age-specific cervical cancer incidence in El Salvador from GLOBOCAN 2018 (Bray et al., 2018). We selected the 50 top-fitting input parameter sets to use in cost-effectiveness analysis as a form of probabilistic sensitivity analysis (Supplementary Figs. 1, 2, and 3; Supplementary Table 1). Results are reported as the mean and range of outcomes across the top 50 parameter sets. Following calibration, we assessed the visual fit of the prevalence of oncogenic HPV in women aged 50 to 59 years in the home-based self-collection study (Maza et al., 2018), as prevalence data in this age group were not available from Phase 2 of the CAPE project.

2.2. Strategies

HPV testing was assumed to target women aged 30 to 59 years. Given that HPV self-collection was not endorsed by the WHO at the

time of the study, and because the careHPV test used in El Salvador is a signal-based assay rather than a PCR-based test—with potentially lower sensitivity among self- versus provider-collected samples (Arbyn et al., 2014)—we assumed that the routine screening interval would be three years for HPV self-collection, compared with five years for clinic-based provider-collection (Maza et al., 2018).

We evaluated the cost-effectiveness of HPV self-collection offered by a health promoter to women at home compared to no screening, as women targeted by self-collection outreach efforts are primarily screening non-attenders who were reluctant to participate in previous screening programs. We also evaluated HPV self-collection for non-attenders as part of a comprehensive screening program in which the vast majority of eligible women receive HPV testing from a provider at a clinic; the comprehensive program was compared to clinic-based provider-collection as a stand-alone program. The pathways of care associated with HPV self- and provider-collection are displayed in Fig. 1. Coverage of clinic-based provider-collection was assumed to be 81%, reflecting screening participation in Phase 2 of the CAPE project (Cremer et al., 2017); coverage of HPV self-collection at home was assumed to be 18% (i.e., 19% of screening-eligible women who were non-attenders multiplied by 94% acceptance of self-collection among non-attenders (Maza et al., 2018)).

We assumed that screening non-attenders would be contacted by a health promoter at home, as in the self-collection study (Maza et al., 2018). During this initial visit, the health promoter would explain the process of self-collection with the use of a visual aid. Women would then be invited to perform self-collection at home. The health promoter would then transport specimens via cold chain to the clinic, where they would be stored until transported to the laboratory for processing. Within several weeks, health promoters would return to the home to provide results to HPV-negative women and refer HPV-positive women to the clinic to receive results and cryotherapy. (While HPV-positive women in the self-collection study were referred directly to colposcopy, we assumed that a national program would follow the same protocol as with HPV-positive women screened at the clinic—i.e., referral to cryotherapy). We assumed HPV-positive women who complied with the

Table 1
Baseline values and ranges for model variables.[a]

Variable (reference)	Baseline value	Sensitivity analysis value
Population coverage of HPV-based screening program (Cremer et al., 2017; Maza et al., 2018)		
Provider-collection	81%	
Self-collection	18%	5%
Results visit compliance (Cremer et al., 2017; Maza et al., 2018)[b]		
Provider-collection	100%	
Self-collection	97%	60%; 80%
Cryotherapy compliance (Cremer et al., 2017; Maza et al., 2018)[b]		
Provider-collection	100%	
Self-collection	97%	60%; 80%
Colposcopy compliance (Cremer et al., 2017; Maza et al., 2018)[b,c]		
Provider-collection	53.6%	
Self-collection	53.6%	39.7%
Treatment compliance following histologic diagnosis of CIN2 (Cremer et al., 2017; Maza et al., 2018)[b,c]		
Provider-collection	52.4%	
Self-collection	52.4%	29.7%
Test sensitivity/specificity for CIN2+ (Jeronimo et al., 2014)		
careHPV (provider-collection)	0.78/0.89	
careHPV (self-collection)	0.67/0.87	0.78/0.89
Test sensitivity/specificity, colposcopy (Cremer et al., 2016)[d]	Threshold of CIN2+ 0.46/0.95	Threshold of CIN1+ 0.98/0.03
Eligibility for cryotherapy (Cremer et al., 2017; Gage et al., 2009)		
No lesion or CIN1	90%	
CIN2	85%	
CIN3	75%	
Cancer	10%	
Effectiveness of cryotherapy to treat CIN2, CIN3 (Sauvaget et al., 2013; Cremer et al., 2010; Campos et al., 2019)[e]	88%	
Proportion of women retaining an HPV infection following cryotherapy (Starks et al., 2014)	15%	
Effectiveness of treatment with cryotherapy or LEEP to treat CIN2, CIN3 following colposcopy (Chirenje et al., 2001)[e]	94%	
Proportion of women retaining an HPV infection following colposcopic diagnosis and treatment (Ryu et al., 2012; Kreimer et al., 2012)	10%	
Direct medical costs (2017 US$)		
careHPV test (provider-collection) (Campos et al., 2015b; Campos et al., 2019)[f]	$8.73	
careHPV test (self-collection)[g]	$11.37	Health promoter time cost: 50%–150% of baseline value Equipment cost: 50%–200% Programmatic cost: 50%–200%
Cryotherapy (clinic) (Campos et al., 2015b; Campos et al., 2019)[e,h]	$11.47	
Colposcopy and biopsy (hospital) (Campos et al., 2015b; Campos et al., 2019)	$89.39	
LEEP (hospital) (Campos et al., 2015b; Campos et al., 2019)	$46.50	
Pap (hospital; follow-up after treatment at hospital) (Campos et al., 2015b; Campos et al., 2019)	$4.36	
Simple hysterectomy	$827	
Direct non-medical costs		
Women's transportation (round-trip, clinic) (Campos et al., 2015b; Campos et al., 2019)	$0.78	50%–150% of baseline value
Women's transportation (round-trip, hospital) (Campos et al., 2015b; Campos et al., 2019)	$3.10	50%–150% of baseline value
Women's transportation (round-trip, cancer center) (Campos et al., 2015b; Campos et al., 2019)	$8.27	50%–150% of baseline value
Women's time costs (Dirección general de estadística y censos (DIGESTYC), 2013)[i]		
Screening visit (provider-collection) (Campos et al., 2015b; Campos et al., 2019)[j]	$5.32	50%–150% of baseline value
Screening visit (self-collection)[k]	$0.76	50%–150% of baseline value

(*continued on next page*)

Table 1 (*continued*)

Variable (reference)	Baseline value	Sensitivity analysis value
Results visit (provider-collection)[l]	$5.25	50%–150% of baseline value
Results/referral visit (self-collection)[m]	$0.13	50%–150% of baseline value
Cryotherapy visit (clinic, provider-collection) (Campos et al., 2015b; Campos et al., 2019)[n]	$0.38	50%–150% of baseline value
Cryotherapy visit (clinic, self-collection)[e,o]	$5.63	50%–150% of baseline value
Cryotherapy (hospital, following colposcopy) (Campos et al., 2015b; Campos et al., 2019)[e,p]	$8.74	50%–150% of baseline value
Colposcopy[q]	$8.98	50%–150% of baseline value
LEEP (Campos et al., 2015b; Campos et al., 2019)[q]	$8.98	50%–150% of baseline value
Simple hysterectomy (Campos et al., 2019)	$54.82	50%–150% of baseline value
Treatment of local cancer (FIGO stages 1a–2a) (Campos et al., 2015b; Campos et al., 2019)[r]	$4570	
Treatment of regional/distant cancer (FIGO stages ≥2b) (Campos et al., 2015b; Campos et al., 2019)[s]	$5481	

[a] CIN: cervical intraepithelial neoplasia; FIGO: Federation Internationale de Gynecologie et Obstetriques; LEEP: loop electrosurgical excision procedure.

[b] Visit compliance is the proportion of women who show up for a recommended visit, of those who attended the previous recommended visit. The study of HPV self-collection in El Salvador followed a different management algorithm (i.e., referral of HPV-positive women to colposcopy) (Maza et al., 2018) than the CAPE project and recent national guidelines (i.e., referral of HPV-positive women to treatment with cryotherapy). Therefore, our base case assumed a high proportion of women complied with the results and cryotherapy visit (similar to the nearly perfect compliance to receiving colposcopy in the self-collection study), but we explored lower values for these parameters in sensitivity analysis. For treatment compliance among women who were determined to be ineligible for same-day cryotherapy, we used point estimates from CAPE Phase 2 data in the base case, and the lower bound of the 95% confidence interval from phase 2 in sensitivity analysis.

[c] Compliance with colposcopy and treatment was only relevant for women who were not deemed eligible for cryotherapy at the clinic.

[d] Test performance characteristics of colposcopy were derived from the worst diagnosis of the local pathologist relative to the worst diagnosis by a quality control pathologist (gold standard) from Phase 2 of CAPE, using the treatment threshold of CIN2+. In sensitivity analysis, we explored the impact of changing the positivity threshold to CIN1+, also based on Phase 2 data.

[e] Cryotherapy was assumed to occur at the clinic for women deemed eligible for cryotherapy. For those deemed ineligible for cryotherapy at the clinic and diagnosed with CIN2+ following colposcopy/biopsy, treatment with cryotherapy, LEEP, or simple hysterectomy was assumed to occur at the hospital. Based on the demonstration project, we assumed that women receiving treatment after histologic confirmation would be treated as follows: < CIN2, 99.6% cryotherapy, 0.3% LEEP, 0.1% simple hysterectomy; CIN2: 92.7% cryotherapy, 4.5% LEEP, 2.7% simple hysterectomy; CIN3: 53.4% cryotherapy, 28.6% LEEP, 18% hysterectomy (WHO, 2013). The effectiveness of cryotherapy includes management of residual disease detected during follow-up. We assumed that women receiving cryotherapy or LEEP would receive follow-up including a Pap test at the clinic or hospital and a colposcopy in the year following treatment, with 1% of women receiving an additional Pap following a positive colposcopy result.

[f] The direct medical cost per woman screened by a provider at the clinic includes 15 min of provider time ($0.89), speculum and sterilization ($0.03), HPV test and collection materials ($6.90), driver time and fuel cost for laboratory transport ($0.25), laboratory personnel time ($0.11), laboratory supplies ($0.54), and programmatic costs (administrative costs, stationary, waste disposal, $0.30).

[g] The direct medical cost per woman screened at home with self-collection offered by a health promoter includes health promoter time and transportation ($3.46), HPV test and collection materials ($6.90), equipment (re-usable visual aid, cooler and icepack for transport, $0.10), driver time and fuel cost for laboratory transport ($0.25), laboratory personnel time ($0.11), laboratory supplies ($0.54), and programmatic costs (administrative costs, stationary, waste disposal, and training costs, $1.48). Unit costs are provided in Supplementary Tables 2, 3, and 4.

[h] On average, we assumed 30 women could be treated per $286 nitrous oxide tank refill.

[i] The average woman's hourly wage was assumed to be $1.52, based on a national survey of household income from 2012 that was adjusted for inflation, assuming 2 earners per household working 40 h per week each.

[j] Includes 15 min of wait time, 15 min of procedure time, and 180 min of round-trip transportation time.

[k] Includes 30 min of procedure time.

[l] Includes 15 min of wait time, 12 min of procedure time, and 180 min of round-trip transportation time.

[m] Includes 5 min of procedure time.

[n] Includes 15 min of procedure time.

[o] Includes 15 min of wait time, 27 min of procedure time, and 180 min of round-trip transportation time.

[p] Includes 150 min of wait time, 15 min of procedure time, and 180 min of round-trip transportation time.

[q] Includes 150 min of wait time, 30 min of procedure time, and 180 min of round-trip transportation time.

[r] Includes direct medical costs of treatment and follow-up, as well as direct non-medical costs of patient and support person time and transport to the National Cancer Institute in San Salvador for treatment, meals/housing during the course of treatment, and direct non-medical costs of patient time and transport to the National Cancer Institute for follow-up (2 Pap tests per year for the first two years following cobalt therapy, then one Pap test per year up to 10 years post-treatment). We assumed 50% of local cancer patients presented with FIGO stage 1a, requiring radical hysterectomy, and 50% of local cancer patients presented with FIGO stage 1b/2a, requiring cobalt therapy followed by 5 chemotherapy sessions followed by brachytherapy. Cancer cost data were collected in 2012 and converted to 2017 US$ using GDP deflators.

[s] Includes direct medical costs of treatment and follow-up, as well as direct non-medical costs of patient and support person time and transport to the National Cancer Institute in San Salvador for treatment, meals/housing during the course of treatment, and direct non-medical costs of patient time and transport to the National Cancer Institute for follow-up (2 Pap tests per year for the first two years following cobalt therapy, then one Pap test per year up to 10 years post-treatment). We assumed all women presenting with FIGO stage ≥2b received cobalt therapy followed by 5 chemotherapy sessions followed by brachytherapy. Cancer cost data were collected in 2012 and converted to 2017 US$ using GDP deflators.

recommended visit were examined visually to determine eligibility for cryotherapy; if eligible, they were treated the same day. If ineligible for cryotherapy, women were referred to colposcopy at a hospital for further diagnosis. Those who attended the colposcopy appointment were referred to treatment according to guidelines if the histological diagnosis was cervical intraepithelial neoplasia grade 2 (CIN2) or higher (CIN2+). Women with a diagnosis < CIN2 were referred back to routine screening.

Clinic-based provider-collection of HPV specimens was assumed to take place at a clinic. Women were scheduled to return to the clinic to receive HPV results within several weeks, at which time HPV-positive women would be visually assessed for cryotherapy; if eligible they would be treated the same-day. If ineligible for cryotherapy, referral to colposcopy and subsequent management would occur just as with the HPV self-collection strategy.

Screening and treatment parameters are displayed in Table 1. Data from CAPE Phase 2 and the self-collection study in the Paracentral region informed screening coverage levels for clinic-based provider-

Table 2
Base case cost, health, and cost-effectiveness outcomes, HPV self-collection for screening non-attenders (El Salvador per capita GDP: US$3890; 50% of per capita GDP: US$1945).[a]

Screening strategy	Reduction in lifetime risk of cervical cancer (%)[b]	Discounted lifetime cost per woman (US$)	Discounted life expectancy (years)	ICER (US$/YLS)
HPV self-collection for screening non-attenders[c]				
No screening	–	25.91 (20.13–32.10)	28.9124 (28.8855–28.9409)	–
HPV self-collection (home)	14.2 (11.9–15.9)	42.08 (36.59–48.20)	28.9258 (28.9024–28.9510)	1210 (950–1730)
HPV screening program, including clinic-based provider and home-based self-collection[d]				
No screening	–	25.91 (20.13–32.10)	28.9124 (28.8855–28.9409)	–
HPV provider-collection (clinic)	59.9 (48.2–68.0)	69.87 (64.96–76.31)	28.9696 (28.9567–28.9834)	770 (580–1140)
HPV provider-collection (clinic) + HPV self-collection (home)	74.0 (60.1–84.0)	86.04 (80.18–94.11)	28.9830 (28.9730–28.9935)	1210 (950–1730)

[a] US$: 2017 United States dollars; YLS: year of life saved. For reduction in cancer risk, discounted lifetime costs, and discounted life expectancy, the mean value and range is reported across 50 input parameter sets; the reported ICER is the ratio of the mean costs divided by the mean effects of one strategy versus another across the 50 sets.
[b] Relative to no screening.
[c] HPV self-collection for screening non-attenders (every 3 years) was assumed to cover 18% of women aged 30 to 59 years.
[d] HPV provider-collection at the clinic (every 5 years) was assumed to cover 81% of women aged 30 to 59 years; HPV self-collection for screening non-attenders (every 3 years) was assumed to cover 18% of women aged 30 to 59 years.

collection and self-collection; the proportion of women who received HPV results and recommended follow-up (assuming compliance with colposcopy following an HPV-positive result in the study was a reasonable proxy for compliance with cryotherapy); eligibility for cryotherapy; and test performance of colposcopy. HPV test performance for each modality was based on a demonstration project of HPV provider- and self-collection in Nicaragua (Cremer et al., 2017; Maza et al., 2018; Jeronimo et al., 2014; Cremer et al., 2016; Gage et al., 2009; Sauvaget et al., 2013; Cremer et al., 2010; Chirenje et al., 2001; Dirección general de estadística y censos (DIGESTYC), 2013; Campos et al., 2015b; Campos et al., 2019;Ryu et al., 2012; Starks et al., 2014; Kreimer et al., 2012).

2.3. Cost data

The costs of HPV testing-based screening with either self-collection or clinic-based provider-collection (in 2017 US$) are presented in Table 1. We included direct medical costs (including staff time, disposable supplies, laboratory, and equipment use); patient time costs associated with travel, waiting, and receiving care; patient transportation costs; and available programmatic costs.

Costs were drawn from the self-sampling study and CAPE Phases 1 and 2, and were estimated using a micro-costing approach informed by the expert opinions of in-country clinicians, MINSAL officials, and representatives at the Cancer Institute in El Salvador (Campos et al., 2015b). Cost and wage data that were originally collected in 2012 US$ were updated to 2017 US$ using GDP deflators (*World Development Indicators*, 2018). The HPV testing cost, which includes the cost of the careHPV test kit, collection device, and laboratory reagents, was updated to $6.90.

Costs pertaining to an HPV self-collection program were estimated from the self-collection feasibility study, and included health promoter time and transportation for screening and results visits; the HPV test kit; equipment, including coolers, ice packs, and re-usable visual aids for patient education (equipment costs were amortized at a rate of 3% over the usable lifespan); and programmatic costs (for training of health promoters, including health promoter and trainer time, supplies, and venue rental). Total programmatic costs were divided by the total number of women screened in the self-collection study to yield a programmatic cost per woman screened (Supplementary Tables 2, 3, and 4).

2.4. Scenario analyses

We explored uncertain parameters involving HPV self-collection in scenario analyses, including coverage; visit compliance; HPV test performance; referral threshold for colposcopy; screening interval; health promoter time and transportation costs; equipment and programmatic costs; treatment costs for screen-positive women; and women's time and transportation costs for screening and preventive treatment.

A checklist for HPV-FRAME reporting standards for modeling HPV and cancer prevention is presented in Supplementary Tables 5 and 6 (Canfell et al., 2019).

3. Results

3.1. Base case: population-level health benefits and cost-effectiveness analysis

Results for the base-case analysis are displayed in Table 2. Compared to no screening for non-attenders, HPV testing with self-collection offered by health promoters in a woman's home and covering 18% of the target population of screening-eligible women reduced the lifetime risk of cervical cancer by 14.2% (range: 11.9%–15.9%). Home-based self-collection of HPV cost $1210 per year of life saved (YLS) compared to no screening, which would be considered very cost-effective relative to El Salvador's per capita GDP ($3890) and 50% of per capita GDP ($1945).

While a screening program based solely on HPV testing with provider-collection at the clinic covering 81% of the target population would reduce cancer by 59.9% (range: 48.2%–68.0%) and cost $770 per YLS (range: $580–$1140 per YLS), incorporating an HPV self-collection intervention with home visits by health promoters for 18% of the population would yield cancer reductions of 74.0% (range: 60.1%–84.0%) at a cost of $1210 per YLS (range: $950–$1730 per YLS). Of note, the range of ICERs from probabilistic analysis fall below the lower benchmark for cost-effectiveness ($1945).

3.2. Scenario analyses: population-level health benefits and cost-effectiveness analysis

Cost-effectiveness results from alternative scenarios (for HPV self-collection compared to no screening) are presented in Fig. 2. When we

Fig. 2. Cost-effectiveness analysis: Base case and sensitivity analysis. Incremental cost-effectiveness ratios for HPV self-collection among women reluctant to screen are presented along the x-axis in 2017 US$ per year of life saved (YLS) for the base-case analysis and univariate sensitivity analyses (y-axis). The bars represent the range of the ICERs for HPV self-collection across the 50 input parameter sets (compared to no screening), with the ICER of the mean costs divided by the mean effects demarcated by a black line. The dashed black line indicates 50% of El Salvador's per capita gross domestic product (GDP) at US$1950, which we considered as a threshold for identifying interventions as very cost-effective.

assumed lower screening uptake (5%) for HPV self-collection to reflect the exclusion of very high-risk areas in the study (base case: 18%), the ICER remained stable ($1210 per YLS) due to proportional changes in costs and life expectancy, but the reduction in cancer risk dropped from 14.2% to 4.0%. Reduced compliance for the visits to receive results and, if recommended, cryotherapy reduced the ICER slightly to $1130 (60% compliance per visit) or $1160 per YLS (80% compliance per visit) due to lower costs, although cancer risk reductions were also slightly lower. When we assumed HPV self-collection test performance was comparable to provider-collection (as it might be with a PCR-based test with a similar cost, as opposed to careHPV), the ICER for self-collection became even more attractive ($1030 per YLS). Colposcopy parameters had little impact on the ICER associated with HPV self-collection, due to the low proportion of women who are referred to colposcopy following determination of ineligibility for cryotherapy.

Health promoter time was the most influential cost, when varied from 50% to 150% in scenario analyses (holding coverage constant). Still, the ICER did not shift by more than $120 per YLS. Health promoter transportation cost, equipment costs, programmatic costs, treatment costs for screen-positive women, and women's time and transportation costs were less influential on cost-effectiveness results.

Screening interval had a substantial impact on the cost-effectiveness of HPV self-collection for screening non-attenders. If non-attenders were offered HPV self-collection only once per lifetime around age 35 years, the cost of the intervention was $280 per YLS (base case: $1210 per YLS). Screening three times per lifetime was valued at $510 per YLS, while screening every 5 years (comparable to the screening interval for HPV provider-collection at the clinic) yielded an ICER of $770 per YLS, which is comparable to a clinic-based HPV provider-collection intervention. Cancer reduction with screening intervals of 5 years was similar to provider-collection at comparable coverage levels (data not shown). ICERs for an integrated program with provider-collection (every 5 years) and HPV self-collection offered to screening non-attenders at different intervals are shown in Fig. 3.

4. Discussion

Using data from an HPV self-collection study and the CAPE Project in the Paracentral Region of El Salvador, we informed a microsimulation model and evaluated the cost-effectiveness of a home-based HPV self-collection intervention for women reluctant to screen at the clinic. The isolated impact of HPV self-collection offered by health promoters to 18% of women aged 30 to 59 years could reduce cervical cancer risk by 14.2% at a cost of $1210 per YLS. This would be considered cost-effective whether the willingness-to-pay threshold is $3890 (El Salvador's per capita GDP) or $1945 (50% of El Salvador's per capita GDP). An integrated cervical cancer screening program comprised of HPV provider-collection at the clinic for 81% of the target population and HPV self-collection for 18% of screening-eligible women yielded a higher ICER ($1210 per YLS) than a program including solely clinic-based screening ($770 per YLS), but this was primarily due to the assumed need for women undergoing self-collection to be screened more frequently. If HPV self-collection was offered to non-attenders every 5 years (comparable to the recommended interval for clinic-based screening), the ICER for HPV self-collection was nearly identical to HPV provider-collection at the clinic.

The self-collection study conducted in El Salvador found that uptake of HPV self-collection among screening non-attenders was 94%, which is comparable to high rates of uptake from studies in Uganda, India, and Mexico (Lazcano-Ponce et al., 2011; Moses et al., 2015; Sowjanya et al., 2009). It is worth noting that high rates of gang-related violence at the time of the study posed a danger to the research team. Municipalities were selected if homicide rates were less than 100 per year between 2010 and 2015, representing 30% of the population of the Paracentral Region. If health promoters are not able to safely access a large number of municipalities to offer self-collection through a national program, or screen-positive women do not feel safe attending the clinic for recommended treatment, coverage and compliance will be much lower than what we assumed in our base case. In a scenario analysis, we assumed uptake rates from the self-collection study could only be achieved for 30% of non-attenders (i.e., 5% uptake in the general

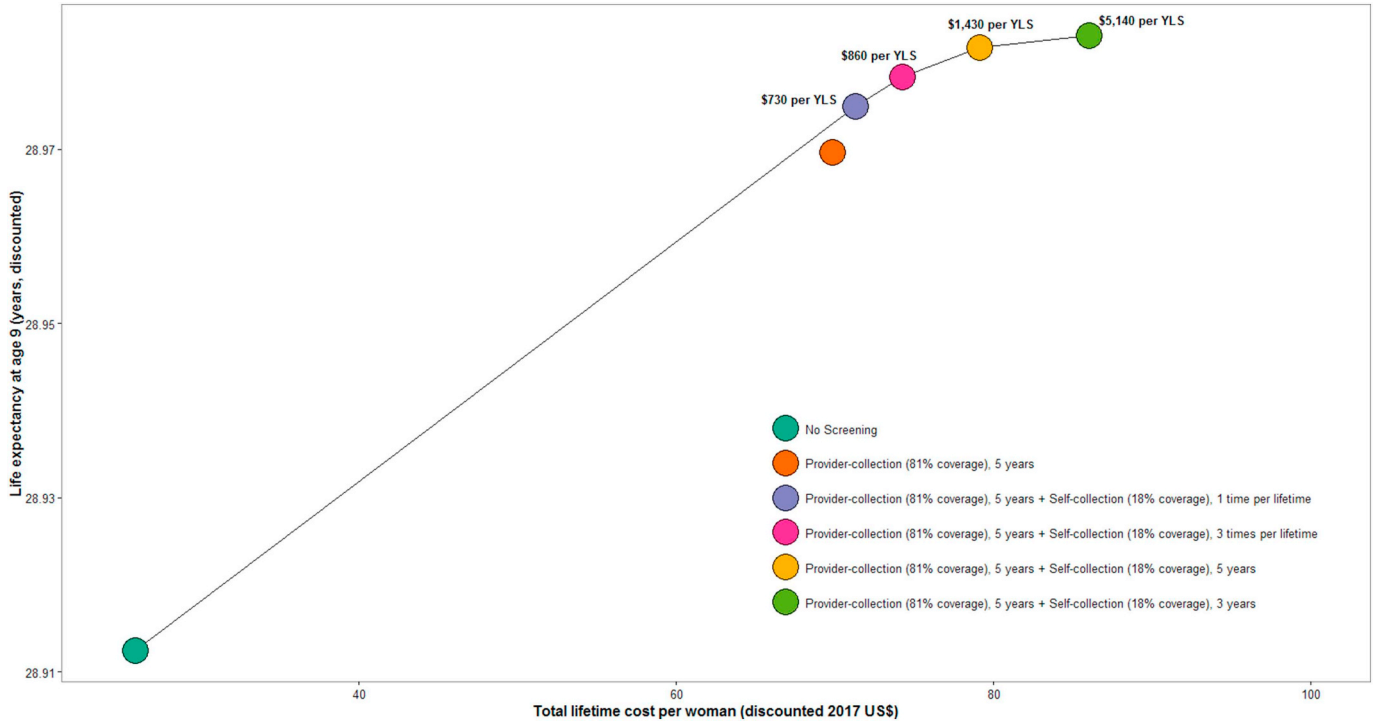

Fig. 3. Cost-effectiveness analysis of an integrated HPV testing-based screening program. The graph displays the discounted lifetime costs (x-axis; in 2017 US$) and life expectancy from age 9 years (y-axis) associated with each screening program for 30 to 59 year-old women (orange marker: clinic-based HPV testing with provider-collection alone very 5 years [81% coverage]; purple marker: provider-collection every 5 years [81% coverage] and HPV self-collection once in a lifetime [18% coverage]; pink marker: provider-collection every 5 years [81% coverage] and HPV self-collection three times in a lifetime [18% coverage]; yellow marker: provider-collection every 5 years [81% coverage] and HPV self-collection every 5 years [18% coverage]; and green marker: provider-collection every 5 years [81% coverage] and HPV self-collection every 3 years [18% coverage]), under base-case assumptions for all other parameters. The cost-effectiveness associated with a change from one strategy to a more costly alternative is represented by the difference in cost divided by the difference in life expectancy associated with the two strategies. The curve indicates the strategies that are efficient because they are more effective and either 1) cost less; or 2) have a more attractive cost-effectiveness ratio than less effective options. The incremental cost-effectiveness ratio (ICER) is the reciprocal of the slope of the line connecting the two strategies under comparison. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

population). While the cost-effectiveness of self-collection remained stable, the reduction in cancer risk was only 4%.

Maza and colleagues found that the most common reasons women mentioned for not attending previous screening appointments included embarrassment at being seen by a male physician (55.6%), believing a lack of symptoms indicated there was no need to attend the clinic (38.9%), believing the test was not necessary (27.5%), and concern that screening would be painful (27.1%) (Maza et al., 2018). Women also cited convenience factors, including inability to find childcare or receive time off of work, and waiting too long at the clinic. Offering home-based self-collection opportunities will likely assuage some of these concerns. Contact with health promoters may offer reassurance and education in response to concerns about the necessity of screening and potential pain. A screening adherence study within the CAPE demonstration project revealed that women who did not attend a screening appointment following an information session were more likely to have a greater number of lifetime sexual partners and had a longer time since previous screening relative to attenders (Alfaro et al., 2015), indicating a potentially higher risk of cervical cancer among these women. Logistical barriers were not significantly associated with non-adherence, but this could in part be due to the high rate of screening adherence (88%), facilitated by health promoters who offered appointment reminders, rescheduling, and assistance with transportation.

There are several limitations to this study. Maza and colleagues assessed the acceptability of an HPV self-collection algorithm that involved referring HPV-positive women to colposcopy, rather than cryotherapy. In theory, cryotherapy is available in more facilities than colposcopy, and thus should be less burdensome for women (Maza et al., 2018). However, we cannot be sure that the 95% of HPV-positive women who accepted colposcopy in the study would also accept cryotherapy in a national program. Scenario analyses in which compliance with cryotherapy was set at 60% and 80% suggested that linkage to treatment had a proportional impact on costs and health benefits; the ICER did not change substantially. Data on program costs for an HPV self-collection intervention were limited to training costs, and may not fully account for quality control measures, development of training and patient education materials, and other costs for rolling out or sustaining the intervention. Personnel and equipment costs were based on the assumption that health promoters relied on their own transportation or buses to reach women's homes, which may not be possible in some regions. We did not consider a potentially greater burden of HPV among women reluctant to screen, as HPV test positivity rates among these women were not significantly higher than among women in Phase 2 of the CAPE project; however, roll-out of a national screening program with a self-collection intervention might encounter areas with a higher burden of disease. Finally, we did not consider the impact of screening with cytology prior to age 30, which is recommended as part of El Salvador's national screening guidelines; we restricted the present analysis to comparing HPV self-collection to no screening for those who were reluctant to screen at the clinic, and the cost-effectiveness of a program with integrated HPV provider- and self-collection for women over age 30 years.

The cost-effectiveness of the HPV screen-and-treat algorithm in El Salvador (using per capita GDP as a threshold) has already been demonstrated, and in the current analysis we evaluate the cost-effectiveness of home-based HPV self-collection facilitated by health promoters (Campos et al., 2019). However, few studies have analyzed the cost-

effectiveness of HPV self-collection in LMIC. A cost-effectiveness analysis of the ASPIRE trial in Uganda found that home-based HPV self-collection facilitated by community health workers would have good value for public health dollars when followed by treatment for HPV-positive women (Mezei et al., 2018). Likewise, a micro-costing exercise and cost-effectiveness analysis of a hypothetical group-based HPV self-collection campaign found that self-collection was an attractive alternative to provider-collection at the clinic if greater uptake could be achieved (Campos et al., 2017). Like the present analysis, previous cost-effectiveness studies have made costing assumptions due to lack of data, as well as assumptions regarding the pathway of care in the particular setting. As countries implementing HPV testing-based screening programs begin to design outreach programs for under- and unscreened women, it is likely that better costing and programmatic data will become available.

5. Conclusions

We conclude that a home-based HPV self-collection intervention for women reluctant to screen is likely to be cost-effective in El Salvador, if reasonable coverage levels can be achieved given safety considerations for health promoters. The infrastructure of health promoters is already in place within communities. Our model-based approach suggests that women who opt to self-collect can be screened at comparable intervals to clinic-based HPV provider-collection (i.e., 5 years), with minimal decrements in health benefits attributable to test performance between collection modalities. As El Salvador continues to scale up HPV-based screening, HPV self-collection offered by health promoters to women in their homes appears to be a feasible, acceptable, effective, and cost-effective means of improving screening uptake and reducing health disparities.

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Author contribution statement

Nicole Campos: Conceptualization, data curation, formal analysis, investigation, methodology, visualization, supervision, writing – original draft. **Karla Alfaro**: Conceptualization, funding acquisition, investigation, writing – reviewing & editing. **Mauricio Maza**: Conceptualization, funding acquisition, investigation, writing – reviewing & editing. **Stephen Sy**: Software, writing – reviewing & editing. **Mario Melendez**: Investigation, writing – reviewing & editing. **Rachel Masch**: Funding acquisition; writing – reviewing & editing. **Montserrat Soler**: Project Administration, writing – reviewing & editing. **Gabriel Conzuelo-Rodriguez**: Formal analysis, writing – reviewing & editing. **Julia C. Gage**: Formal analysis, investigation, data curation, writing – reviewing & editing. **Todd A. Alonzo**: writing – reviewing & editing. **Philip E. Castle**: Investigation, writing – reviewing & editing. **Juan C. Felix**: writing – reviewing & editing. **Miriam Cremer**: Conceptualization, investigation, resources, writing – reviewing & editing, funding acquisition. **Jane J. Kim**: Conceptualization, methodology, investigation, resources, supervision, writing – reviewing & editing.

Declaration of competing interest

Authors Maza, Alfaro, Sy, Melendez, Masch, Soler, Conzuelo-Rodriguez, Alonzo, and Felix declare no conflict of interest. Dr. Campos was paid as a consultant by Basic Health International to pursue this study. Dr. Gage declares that the National Cancer Institute has received cervical cytology and HPV testing results for independent NCI-directed studies at reduced or no cost from Roche and Becton Dickinson outside the submitted work. Dr. Castle has received HPV tests and assays at a reduced or no cost for research from Becton-Dickinson, Roche, Cepheid, and Arbor Vita Corporation. Dr. Cremer is the president and founder of Basic Health International, the non-governmental organization that funded this study, and has received fees from the Merck Speakers Bureau. Dr. Kim was paid as a consultant by Basic Health International to pursue this study. The El Salvador Ministry of Health received donated careHPV tests and equipment from Qiagen Cares.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2019.105931.

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