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Clinical trial to implementation: Cost and effectiveness considerations for scaling up cervical cancer screening in low- and middle-income countries

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ABSTRACT

Cervical cancer is preventable and early diagnosis is possible using low-cost technologies. Despite the strong evidence base for cervical cancer screening programs, their implementation has been slow in limited-resource countries where the cancer burden is high. In this study we provide a framework for systematically evaluating costs and effectiveness in order to translate clinical study findings to guide implementation of screening programs to maximize benefits in the real-world setting. Comparing the total cost of screening can be misleading, as the resources expended on specific program activities can have direct impact across multiple dimensions including access, quality, and adherence to care; these dimensions, in turn, can affect both overall health care cost and program effectiveness. Therefore, it is important to use activity-based costs and detailed performance indicators to evaluate both screening trials and pilot studies to ensure that large-scale implementation projects are designed and optimally resourced to achieve targeted program effectiveness and outcomes.

1. Background

Cervical cancer poses a significant burden to women worldwide, with 528,000 new cases and 266,000 deaths in 2012 [1]. Almost 70% of the global burden is experienced in resource-constrained countries in Asia, Africa, and South America, and more than one-fifth of all new cases are diagnosed in India [2]. Mortality from cervical cancer is the most common cause of cancer-related deaths among women in many regions in rural South Asia and sub-Saharan Africa [3–5]. Cervical cancer affects women during their most productive years, as most are diagnosed in their 40s and 50s, and therefore it adversely affects women's families as well.

Cervical cancer is preventable and early diagnosis is possible using low-cost technologies. The World Health Organization's guidelines for screening and treating cervical cancer provide recommendations for screening programs on the basis of resource availability. Recommended screening approaches include human papillomavirus (HPV) testing, cytology (Pap test), and visual inspection with acetic acid (VIA) [6]. Cytology-based screening programs are generally not an optimal strategy in low- and middle-income countries because the high cost of establishing and providing quality-assured Pap tests limits the ability to establish large-scale programs. The see-and-treat approach using VIA or rapid HPV test is favored as it minimizes loss to follow-up; women who have a positive test are offered immediate treatment for premalignant lesions or cervical intraepithelial neoplasia (CIN) without histologically confirmed diagnosis [7–9].

The knowledge base exists to prevent and screen for cervical cancer in the low-resource setting, but, unfortunately, large-scale sustainable screening programs are very limited [10]. The establishment of screening programs in high-income countries has resulted in a dramatic decrease in the incidence of cervical cancer. From 1955 through 1992, the rate of cervical cancer deaths in the United States declined by nearly 70%, and it continued declining more gradually to 2003 before stabilizing [11]. The overall decline is

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mainly attributed to the increased use of the Pap test, which allowed for treatment of precancerous lesions to prevent progression to cervical cancer [12]. Screening coverage has generally been between 70% and 80% among women in the United States, but, unfortunately, screening rates are extremely low in countries that currently have high cervical cancer incidence rates [13,14].

There is thus an urgent need to implement approaches already available for prevention and early detection of cervical cancer in low- and middle-income countries. Methodological approaches and tools are required to translate clinical study findings to facilitate large-scale implementation. Interaction between cost and effectiveness in program implementation is complex, and failures along the continuum of care can have a substantial impact on both the overall effectiveness of the screening program and the cost to the health care system. Modeling studies provide evidence on whether the overall approach or test selected is cost-effective, but these studies have not generally provided practical guidance on the optimal screening delivery strategies for implementing programs [15–17]. A more detailed review of activity-based costs and their impact on program outcomes is required.

The objective of this study is to provide a framework for systematically evaluating costs and effectiveness metrics in order to extrapolate findings from screening trials to guide implementation of programs to maximize benefits in the real-world setting. Costs and outcomes from a clinical trial setting may not be directly generalizable to large-scale screening program implementation, and understanding these differences can help us design programs with optimal features and functionality. We draw upon the experiences gained and lessons learned in clinical trials and a large-scale pilot in India to provide the empirical evidence base to guide the scale-up and integration of cervical cancer screening into routine health care practice.

2. Clinical trials to implementing of cervical cancer screening: India as the case study

Several of the large screening trials that have established the evidence base for cervical cancer screening in the low-resource setting have taken place in India. A cluster-randomized, controlled trial involving about 80,000 women, begun in 1999 in the Dindigul district in southern India, found that a single round of VIA reduced cervical cancer incidence and mortality by about a third [18]. Furthermore, another randomized, controlled trial conducted among 150,000 women in the slums of Mumbai showed that biennial screening for cervical cancer using VIA performed by trained nonmedical personnel reduced cervical cancer mortality by 31% [19]. A third trial in the Osmanabad district in India, which compared the efficacy of screening using HPV testing, cytology, and VIA through random assignment of approximately 132,000 women in 52 clusters of villages, reported a significant difference in mortality rate for the HPV-tested group compared with those receiving standard care [20].

The state government of Tamil Nadu in southern India, with the support of the World Bank, launched the Tamil Nadu Health System Project (TNHSP) as a 5-year demonstration project in 2005. The major elements of this initiative were health promotion and pilot testing of screening and control interventions for noncommunicable diseases. One of the clinically based interventions that was pilot tested in two districts, Thanjavur and Theni, was the use of visual inspection (using acetic acid or Lugol's iodine) to screen for cervical cancer, following the evidence generated in the randomized trial in Dindigul district [18]. The goals of the cervical cancer program were to raise community awareness, promote early detection by offering routine screening to women ages of 30–60 years, and offer appropriate referrals and treatment. From 2007 through 2010, the program screened nearly 500,000 women, which resulted in more than 20,000 positive tests that required follow-up evaluation [21]. The state of Tamil Nadu has now scaled up the cervical cancer screening program to include the entire state [22]. Other cervical cancer implementation projects are ongoing in India (Sikkim) and other low- and middle-income countries in Asia (Bangladesh, Thailand), Africa (Zambia), and South America (Colombia) [23–25]. The TNHSP, though, is a unique large-scale pilot that allows for the critical assessment of the cost and effectiveness of translating research into practice on the basis of findings from a randomized clinical trial performed in the same setting.

3. Framework for planning and implementing cervical cancer screening

Fig. 1 presents the key attributes and cost parameters that should be evaluated to guide the scale-up of cervical cancer screening. A multilevel perspective that includes the health system, the screening program, and the community will allow for a comprehensive assessment of barriers and facilitators and enable cost assessment from the viewpoint of multiple stakeholders. "Health system," in this context, includes facilities, health care providers, medical supplies, equipment and medications, and information systems. The intermediate measures of program success are those related to access to care, quality of care, and adherence to care.

3.1. Access to care

Access to health care refers to the ease with which an individual can obtain needed medical services—in this case, cervical cancer screening and follow-up services related to diagnosis, treatment, survivorship, and palliative care [26]. Ensuring adequate capacity along the continuum of care is critical, as any screening program will be effective only if appropriate interventions are provided to those with premalignant lesions to prevent cervical cancer and comprehensive cancer treatments are delivered to those diagnosed with malignant lesions to improve survival. Many factors can affect access, including distance to health services, cost of travel, and wait time at health facilities [27,28]. The process and health care infrastructure used for screening delivery and follow-up care can affect patient access and overall effectiveness of the program. In the clinical trials in India, screening clinics in targeted geographic locations have been used to enhance recruitment, and transportation was often provided to facilitate access [18–20]. In the VIA trial in rural Tamil Nadu, colposcopies, biopsies, and cryotherapy were performed in the screening clinics, and a see-and-treat approach was used when appropriate [18]. On the other hand, in the TNHSP cervical cancer pilot, screening was embedded within the health care infrastructure and offered at 85 primary health centers (PHCs) and 21 government hospitals, whereas colposcopy was performed in 3 facilities in each of the two districts [21]. PHCs are the cornerstone of rural health care in India, with each center covering a population of about 100,000 spread over approximately 100 villages. The mission of PHCs is to serve as the initial triage center for the health care needs of the rural population, so offering cervical cancer screening through these centers is a logical approach for scaling up screening using the existing health care infrastructure. The differences between the approaches used in the clinical trial setting and in the scale-up of cervical cancer screening highlight the importance of rigorous pilot studies before full-scale implementation.

3.2. Quality of care

There are many definitions of quality of care, but a frequently used definition from the U.S. Institute of Medicine (IOM) is the degree to which health services for individuals and populations