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Back from the Future: Rational Accountabilities for Cytopathology in Pap Test Cervical Cancer Screening Arising from Covid19

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Dear Editor,

The post-Covid19 landscape of cervical cancer (CxCa) prevention and management may become unrecognizable as prior to March 2020; but the new dynamics ought to inspire rational considerations. Other tragedies aside, Covid19 has impacted CxCa screening worldwide and will inadvertently reshape cytopathology with novel accountabilities. The discipline seems primed for metamorphosis: broader dimensions and a renewed identity; inter alia, a time of reckoning for Pap test screening and organizational recalculation and repositioning.

Covid19 must spawn progress. It has uncovered the magnitude of accomplishment possible when knowhow and willpower are mobilized in unison. But as seen for other sectors, cytopathology too needs to be multidimensional, responsive, and plastic; consistently in tune with greater events beyond the intrinsic nuances. After all, the Pap test arose from societal and scientific tectonics over 40 years [1]. After early experimental work by Dr. George N. Papanicolaou in 1917 [2], the Pap test was refined by 1945 [3, 4], coined, and promoted by the American Cancer Society (ACS) in 1948 [5], then launched into mainstream healthcare in USA by 1957, when *Acta Cytologica* also formalized to catalogue progress [2, 5].

The Pap test is the most successful cancer screening test. Nations adopting organized Pap test CxCa screening witnessed 70% reductions in cases and deaths since 1957 [5]. But the steady-state momentum in progress, mainly in developed nations, halted following declaration of the Covid19 pandemic by the World Health Organization (WHO) on March 11, 2020 [6]. Although, in 2018, the WHO had announced shocking deductions: one woman died of CxCa every 2 min worldwide [7, 8]. Inevitable deaths as these pose poignant dilemmas however when CxCa is deemed preventable in women given vaccines for human papillomavirus (HPV) and the proven Pap test. Such paradoxes evoke watershed instances for organizations and stakeholders. As the ACS endorsed the Pap test in 1948 under Dr. Charles S. Cameron, the WHO stood equally compelled in May 2018. Under Dr. Tedros A. Ghebreyesus, it unveiled an assault on CxCa branded as a *Call to Action* in its 71st World Health Assembly [9], a banner initiative for the *United Nations' Global Joint Programme on Cervical Cancer Prevention and Control* [7]. The WHO prompted member states toward decision-making and healthcare optimization for CxCa elimination by 2030. The WHO's stance was ambitious, and nothing short of titanic, yet conjures energy towards an achievable goal given cumulative knowledge of CxCa etiology, natural pathobiology, and disease prevention possible through targeted Pap testing [5].

The data supporting the WHO's *Call to Action* is problematic [10, 11]. Nearly 570,000 women had CxCa in 2018 worldwide, and 311,000 died of the disease [8]. Of this burden, 51% of cases occurred in lower middle-income countries (LMICs) in sub-Saharan Africa [10]. Inversely,

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85% of the 311,000 deaths occurred in LMICs – an 18-fold differential relative to high-income nations [8]. Furthermore, whereas 60% of women were screened for CxCa in developed nations, only 20% were in LMICs given multifaceted disparities [8, 10].

In its *2013 Guidance Note*, for 2012, the WHO warned of a staggering 1 billion women worldwide, aged 30–49, who have never been screened [12]. Also for 2012, Gaffney et al. [8] reported 8 million women, aged 21–65, were never screened (*in the preceding 5 years*) in the USA. Additional paradoxes arise, however. The 311,000 global deaths in 2018 occurred despite screening for CxCa, HPV vaccination, and effective treatment in high-income nations [13]. Therefore, although estimates, these data brand CxCa a disease skewed against under-served or unserved women regardless of nation. Unsurprisingly, CxCa remains the 4th most frequent cancer in women globally albeit preventable [8]!

In *United Nations News*, the WHO's Assistant Director-General, Dr. Princess Nothemba Simelela, reflected on modeling correcting for global population growth trends projecting a 22.8% increase in cases to 700,000 by 2030, but a disproportionate 28.6% increase in mortality [14]. As such, trajectories for CxCa deaths seem to continue rising exponentially if the scale and scope of women's healthcare remain in a steady-state, as was status quo prior to Covid19 [10, 13]. Accordingly, in January 2019, the WHO's Executive Board motioned Dr. Ghebreyesus to produce strategies with explicit targets for the *Call to Action* [10]. The *Cervical Cancer Elimination Modelling Consortium* (CCEMC) was thus assembled, tasked to study scenarios with 4 bases [10]: (i) What elimination threshold should be set? (ii) What prevention strategies facilitate elimination? (iii) When could elimination be reached by different countries?, and (iv) How many cases may be averted? From the CCEMC's results, the WHO retrenched in its 73rd World Health Assembly in August 2020 [10, 15, 16] – amid devastating waves of Covid19 ambling throughout humanity.

The CCEMC's collaborators considered 3 models specifically for 78 of the highest disease-burdened LMICs [10, 15]. They calculated variations between extent of HPV vaccination and frequency of lifetime cervical screening on 2 assumptions: (i) All girls are HPV vaccinated by age 15 with 90% coverage and 100% lifetime protection for HPV types 16, 18, 31, 33, 45, 52 and 58; and (ii) HPV DNA cervical screening once or twice per lifetime at age 35 and 45, increasing uptakes from 45% in 2023 to 90% in 2045 onwards [10]. A disease elimination threshold set at ≤4 cases per 100,000 women followed the definition of a rare cancer; also, as some developed nations achieved this milestone through successful mass screening practices [5, 10].

Brisson et al. [10] concluded 40% of sub-Saharan LMICs would not achieve CxCa elimination by 2030 through girls-only HPV vaccination solely, asserting LMICs with CxCa rates of >25 per 100,000 women would face significant obstacles without Pap test screening. Also, that 90% girls-only HPV vaccination coverage alone may lead to disease elimination between 2059 and 2102. Thus, prophylaxis through girls-only HPV vaccination would need to reach at least 90% of girls aged 9–14 augmented by twice-lifetime cervical screening to accelerate disease elimination to the 2030 target [10].

Accordingly, the WHO's strategy is tri-flanked, proposing: (i) 90% of girls *immunized* for HPV by age 15; (ii) 70% of women *screened with an effective screening test* by age 35 with follow-up screening by age 45; and (iii) 90% of women with confirmed cervical neoplasia *treated judiciously*. Irrefutably a tall order. But such maneuvering within increasingly complex landscapes of shifting public health priorities demands bold leadership to sustain an ethical focus on CxCa. The WHO's resolutions were thus endorsed by 194 member states in its 73rd World Health Assembly and ratified in November 2020 [10, 15, 16]. Meanwhile, for 2020, the estimated global CxCa burden after Sung et al. [17] had increased to 604,000 women, with 342,000 deaths. These figures translate into a 6% increase in CxCa incidence within a 2-year period: 2018–2020; but a 10% increase in mortality, respectively. Obviously, these figures cannot possibly account for post-Covid19 repercussions, hence gross under-estimations at best. Finally, Canfell et al. [15] estimated 99% reductions in CxCa mortality over the next century with 62 million lives saved, assuming adherence to the 90-70-90 strategy.

But realities of CxCa are as complicated as diverse. In Canada, with universal, programmatic Pap test screening since 1949, the mean rate of CxCa is 5.5 per 100,000 women [18]. In Eswatini, a South African nation lacking national screening, it is 84.5 [18, 19] – an astonishing 15.4-fold differential. Yet in the USA, CxCa remains the 2nd leading cause of cancer deaths in women aged 20–39, with 10 premature deaths weekly [20]. Unquestionably, whereas all nations will face comparable challenges given the WHO's propositions, some may face impassable obstacles to progress.

After Mar 2020, Covid19 brought Pap testing to a standstill in developed nations due to lockdowns, clinical restrictions, and de-prioritizations. Women and medicine fell back to the early 20th Century when CxCa pre-

vention was a mystery [5]. Funding has been reworked to stem economic collapse, and for urgent production and rollout of vaccines against Covid19 [21]. Elective and emergency surgeries were postponed leaving cancer patients disadvantaged without diagnostics or treatment; a crisis has ensued [22]. In India, the 2nd most populous nation of 1.38 billion people, CxCa screening was reduced to under 25% of normal capacity with utterly unpredictable clinical ramifications [23]. But despite the perils, Canada followed suit: The *Canadian Partnership against Cancer* espoused the *Call to Action* advocating an ambitious 90-90-90 strategy for CxCa elimination by 2040 [24]. It cannot be inconceivable that a future CxCa pandemic is now gathering potency.

Nevertheless, clinical strategies need to be plastic subject to evidence-based evolution. The WHO's 90-70-90 strategy may need reevaluation relative to economic and feasibility factors in any state or region. But the elemental aim of any CxCa screening practice remains the detection of abnormal epithelial cells, ideally those reflecting treatable precancers before invasion [25]. And against this tenet, HPV DNA primary screening may not be the *panacea* alleged. While highly sensitive, HPV DNA primary screening merely reveals infection by high-risk HPV not necessarily excisable lesions. Schiffman et al. [25] concluded that the true value of HPV DNA primary screening is uncertain since a positive HPV test reflecting a developed CxCa may not lead to disease prevention. More confounding is the likelihood of HPV-negative, cytology-positive CxCa cases; thus, the diagnostic value embedded in co-testing Pap test models [25]. Work by Farnsworth et al. [26] from Australia's HPV-based CxCa screening algorithm with reflex cytology studied diagnostic findings of 2,300 women referred to colposcopy after initial HPV-positive screening tests. High-grade lesions were confirmed in 24.3% of these women underscoring the benefits through cell-morphology-based co-testing, and the potential deficits in HPV DNA screening. Related studies emphasize the need to minimize false-positives arising from HPV DNA screening to avert harms to women, such as clinical overreaction, overtreatment, and psychological distress – all associated with profound yet avertable societal costs [27].

HPV-induced cervical pathobiology is furthermore confounding. Whereas HPV vaccination would seem the ultimate approach for disease prevention, decades may span before clinical impact is evident assuming optimal, widespread immunization [28]. Yet the prevailing challenge remains: How to manage women following positive HPV DNA screening when up to 90% of HPV infections may regress or immunologically clear within a 5-year period [28]. Therefore, of critical importance, is how to distinguish between HPV-positive women likely to develop identifiable and thus excisable cervical precancers to sustain disease prevention, from those women with a low probability of developing cervical lesions albeit HPV-positive [28]. The relatively high false-positivity rate associated with HPV DNA testing for high-grade cervical lesions presents a challenge today which may be resolved in the future as more reliable molecular tests are developed to augment screening objectives [29].

Pertaining to the aforementioned dilemmas, perplexing is the thought of forewarning papers appearing soon after introduction of the Bethesda Reporting System (TBS) in 1988 [30, 31]. In 1992, through a European perspective, Syrjanen et al. [30] argued that by incorporating koilocytosis amongst the intraepithelial lesions in the TBS may lead to HPV DNA typing for diagnosis; likewise, to negligible clinical benefit due to the ubiquity and natural pathobiology of low-risk HPV infections, thus potential overtreatment, and undue cost. Their concerns follow data suggesting HPV typing has limited prognostic value in predicting lesion behavior. Whereas HPV 16 lesions carry a 5-fold risk of disease progression relative to HPV 6 or 11, they may undergo natural regression, and 40% of HSIL lesions may ultimately regress without treatment if followed long enough [30]. Similarly, in 1993, Koss [31] stated: "*…there is no evidence that a woman bearer of a high-risk virus will necessarily develop a neoplastic lesion. Because the infection* per se *cannot be cured, testing for viral types, in my judgement at least, only will increase the costs of screening without tangible benefits to society but with high levels of anxiety generated in women testing positive but disease-free*." Follow-up reports in 2000 by Syrjanen [32] based on the remarkable Pap smear screening outcomes experienced in Finland since 1960, and by Miller et al. [33], underscore the proven utility in conventional Pap testing to detect abnormal epithelial cells from cervical precursor lesions, to thus facilitate appropriate colposcopy and disease prevention with least possible overall expense. Collectively, these authors, including the corresponding author, advocate continuation of the time-honored screening Pap test against yet unproven methods, and most particularly in clinical settings with scarce financial resources. This position also fulfills the WHO's rationale for an "*effective screening test*" in the 90-70-90 strategy.

Real-world progress towards CxCa elimination obviously rests on prudent funding and rational CxCa screening. This has abundant relevance. Less than 30% of sub-

Saharan LMICs have introduced HPV vaccination because of unaffordability, compared to 85% in high-income nations [10]. In India, Basu et al. [34] claim long-term protection from 1-dose HPV 16/18 vaccination may supplant the 3-dose vaccinations to protect against 70% of CxCa to maximize healthcare investment and earn valuable time; yet, the remaining 30% of malignancy would remain a threat. As nations cope with alternating waves of Covid19 into 2022, financial disparities may worsen in LMICs with reallocation of foreign-aid funds [22]. Considering the realities of cervical carcinogenesis, HPV DNA primary screening is justifiably questioned, and perhaps the least affordable of screening modalities for LMICs. And cost-benefit-ratio deliberations must also include the variable of time – as 2030 and beyond *are* inevitable.

The stakes were never higher, nor the need to recover lost ground more persuasive. Years of progress in CxCa prevention since 1957 are at risk of reversal. But as the Pap test's *forte* is the detection of silent, treatable, early CxCa, then medical establishments harness a rare opportunity to upend chains of events and surpass ambitious targets or calamities. The Pap test is the linkage between HPV vaccination and treatment in the 90-70-90 strategy, hence the intermediary safety net: it may capture unimmunized women developing silent lesions; it may also identify women that can evade palliative care by revealing excisable precancers. Despite its limitations, the Pap test may perform a crucial balancing act in the most needful of nations. But any recharting ought to consider an empirical review of the armamentarium for selective application; precisely where the proven, relatively cost-effective Pap smear test may prove ideal. Fortunately, Covid19 has also revealed the existence of a mature, exploitable Internet infrastructure, one that may foster greater CxCa screening outcomes globally through digital technology.

The corresponding author appeals for organizational readiness and proactivity. Post-Covid19 cytopathology will arise anew and may be required to drive: *Political leveraging*; *Public healthcare advocacy*; *Effective economics of practice*; *Promotion and application of reengineered screening practices based on CxCa pathobiology, method track record, and specific nations' needs*; also: *Unyielding leadership and partnership to assure equitable screening.*

It is the author's conviction that passive reversion to status quo, to the steady-state of CxCa management prior to 2020 is not a viable option. And in this spirit, every means ought to be rationalized, quantified, and applied to prevent a preventable cancer in women through a global lens. For doing otherwise, in view of the upcoming post-Covid19 realities and unknowns, would appear to be utterly unethical.

Conflict of Interest Statement

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