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Cervical screening during the COVID-19 pandemic: optimising recovery strategies

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Disruptions to cancer screening services have been experienced in most settings as a consequence of the COVID-19 pandemic. Ideally, programmes would resolve backlogs by temporarily expanding capacity; however, in practice, this is often not possible. We aim to inform the deliberations of decision makers in high-income settings regarding their cervical cancer screening policy response. We caution against performance measures that rely solely on restoring testing volumes to pre-pandemic levels because they will be less effective at mitigating excess cancer diagnoses than will targeted measures. These measures might exacerbate pre-existing inequalities in accessing cervical screening by disregarding the risk profile of the individuals attending. Modelling of cervical screening outcomes before and during the pandemic supports risk-based strategies as the most effective way for screening services to recover. The degree to which screening is organised will determine the feasibility of deploying some risk-based strategies, but implementation of age-based risk stratification should be universally feasible.

Introduction

Guidelines for cancer screening programmes are usually made after systematic and careful consideration of the best available evidence to ensure high-quality care and to reduce variability in clinical practice. However, the onset of the COVID-19 pandemic required an immediate response at a time when the duration of the crisis could not be forecast and the nature of the pathogen was still largely unknown. In most settings, the consequence of this situation was a time-limited suspension of services.¹ These disruptions are expected to result in an excess of advanced cancer diagnoses and deaths in the coming years.²⁻⁵

Screening activity has now resumed to an extent in many countries; however, subsequent population-wide COVID-19 outbreaks continue to disrupt health-care provision. Despite the approval of several safe and highly effective COVID-19 vaccines, supply constraints have delayed their roll-out. To date, only 6·5 in every 100 people worldwide have received a COVID-19 vaccine.⁶ Therefore, the current disruptions to health care in general are likely to continue for some time. This situation is unique, and the complex health-care networks spanning primary, secondary, and tertiary care needed for cancer screening programmes require guidance on recovery strategies for resuming routine cervical cancer screening.

We aim to inform the deliberations of decision makers in high-income countries regarding their region-specific policy responses. We draw on our multidisciplinary experience as epidemiologists and simulation modellers to consider recovery strategies for cervical screening that balance the strain on services while minimising the impact on the incidence of and mortality from cervical cancer. We focus on how cervical screening programmes are organised, given the probable impact of such organisational characteristics on programme resilience and the ability to implement efficient and equitable recovery strategies. In this Viewpoint, we outline the policy problem for cervical screening posed by

COVID-19, discuss the relevance of screening programme organisation, and consider effective screening recovery strategies.

The COVID-19 problem

Optimising cervical screening involves finding a set of recommendations—on the target age range, screening interval, and clinical follow-up after positive screens—that balances minimising the population risk of disease with the impact on resources, costs, and quality of life. Re-establishing screening in response to the COVID-19 disruption requires the same considerations, but changes in resource availability and in women's willingness and ability to undergo screening should also be taken into account.

Disruption to primary screening during 2020 means that many women might now be overdue for screening. Diagnostic follow-up and surveillance activities have been disrupted too, delaying investigation for individuals known to be at high risk. Even where services have resumed, capacity might be reduced due to the need for social distancing and additional time associated with using personal protective equipment.

COVID-19 also imposes indirect capacity constraints when consumables, equipment, and staff used in screening are redeployed to tackling the pandemic.⁷ Tests for human papillomavirus (HPV) and COVID-19 have reagents and consumables in common, meaning they compete for limited resources. In Canada, for example, the pandemic has diverted common screening and laboratory resources to COVID-19 testing, causing potential delays to the roll-out of primary HPV testing in different provinces and territories (Peacock S, unpublished).

Ideally, programmes would resolve the backlog of deferred screening and diagnostic appointments by temporarily expanding capacity. Although this approach might be possible to an extent in programmes that use primary HPV testing (because testing is largely automated), key components of any screening programme, such as

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cytology and colposcopy, require a skilled workforce that cannot be expanded quickly and, therefore, represent system bottlenecks. Even where screening staff have responded to the capacity challenge by working overtime, the potential for burnout means that this is only a limited solution.

Although high levels of screening activity could be seen as evidence of a successful re-commencement of the programme, focusing on re-establishing services without considering how best to target capacity runs the risk of overwhelming the system, while failing to maximise the desired outcome of cancer prevention. Instead, if those responsible for screening policy are willing to prioritise individuals at highest risk during the recovery phase, then they are likely to better ameliorate the long-term consequences of COVID-19. Nevertheless, prioritisation of constrained capacity requires trade-offs, and those trade-offs are always associated with opportunity costs. Prioritising services for women at highest risk might require an increase in the interval between screens for some women at low risk. Another available policy lever to achieve risk-based prioritisation of scarce capacity is to use targeted screening awareness campaigns to encourage re-engagement of specific groups of women, as programmes recover.

Relevance of context

Due to several unique characteristics (eg, the very long detectable pre-invasive phase),⁸ it is expected that cervical cancer will be less affected by screening delays related to COVID-19 than will breast or colorectal cancers.⁹ In most cases, cervical cancer screening works by preventing cancer from developing at all by identifying and treating precancerous lesions. In high-income countries, the long-standing availability of cervical cancer screening and the introduction of population-based HPV vaccination in the late 2000s have decreased the absolute burden of disease well below that of breast and bowel cancer.¹⁰ Nevertheless, the current disruption associated with the pandemic threatens to derail WHO's global strategy to accelerate the elimination of cervical cancer as a public health problem.¹¹ Screening and the timely treatment of any detected disease form two of the three pillars of this strategy.

Cervical cancer screening programmes have always differed in various ways. For example, on one hand, Norway, Sweden, Italy, the UK,^{12,13} and Australia¹⁴ have introduced population-based screening programmes with organised call-recall systems relying on registries for information on the women's previous screening history. On the other hand, countries such as Japan and Germany do not have national screening registries and instead operate on an opportunistic basis.^{13,15} Some programmes have mainly offered screening through primary care, whereas others have delivered it through specialist services, such as gynaecology.^{12,16} Some programmes have started replacing cytology with

HPV testing as the primary screening method. This approach has affected the laboratory landscape; for example, HPV testing is completed in an automated way that allows for economies of scale and larger laboratories with smaller workforces.¹⁷ Furthermore, this approach has defined new triage processes,¹⁸ which tend to be complex. Currently, there is no single-triage approach that stratifies risk sufficiently to allow an immediate binary decision between either colposcopy referral or a return to routine screening following a primary HPV-positive test.¹⁹ Hence, follow-up of HPV-positive women with triage findings of low severity (eg, negative cytology or infection with HPV types other than 16 or 18) often involves surveillance that might span several years before a decision is made whether to refer the individual to diagnostic colposcopy or to return them to routine screening. In cytology-based programmes, the proportion of women in this intermediate group under surveillance tends to be small or might not even exist at all.²⁰

In countries with cytology-based screening programmes, test sensitivity has been shown to be highly variable.²¹ In particular, test performance depends on the quality of training of cytology specialists and the quality assurance of the laboratory testing. Programmes also differ in terms of participation, both in primary screening and in follow-up, which is often related to whether or not personal invitations to screen are offered.^{22,23} Programmes with lower coverage will have less impact on cervical cancer incidence than will those with higher coverage. Consequently, where participation had already been low before the pandemic, the COVID-19 disruption will probably have a smaller negative impact than in programmes with good screening participation, in which the gains from screening had been higher.

Organisation and screening performance will influence how resilient a screening programme can be to the COVID-19 disruption, and what the feasible or optimal policy response might be. The heterogeneity of the programmes, as well as the health-care systems in which they function, probably means that there is no single optimal policy response for all countries.

Optimising responses

Some settings have resumed their screening services. Comparing testing volumes before and after the pandemic might provide high-level insights into how many women have missed screening visits; however, this metric will neither reveal nor ensure that those women at highest risk or the most susceptible to cervical cancer are being screened. Potential recovery strategies and their differing advantages and disadvantages are summarised in the table.

To prioritise effectively, a better understanding of the underlying disease risks among groups of women who are less likely to resume attending their screening or follow-up appointments is essential. Immunosuppressed

women, such as organ transplant recipients, who are shielding due to COVID-19 are at increased risk of developing cervical (pre)cancer.^{25,26} Women from an economically disadvantaged background are also at higher risk of developing COVID-19 due to circumstances such as crowded housing or employment that either cannot be done from home or, often, is done in places where it is difficult to maintain physical distance.²⁷ Even before the pandemic, these women were less likely to be screened according to best practice protocol, more likely to miss screening, and more likely to harbour cervical lesions requiring treatment than were women from higher socioeconomic groups.^{28–30} The hardship imposed by COVID-19 due to, for example, loss of employment and insurance, an increasing difficulty in being able to secure a face-to-face appointment in primary care, and a temporarily decreased focus on non-COVID-19 preventive health, might push screening participation further down the individual's priority list. Identifying and engaging these women in the recovery phase will be challenging and will probably require more thoughtful communication strategies than just simple reminders.^{31,32}

Programmes that have relied on personalised invitations are in a good position to adopt a targeted reintroduction of testing. In this case, the optimal allocation of scarce testing capacity could start with extending invitations to women

who are most likely to benefit from early detection. For example, invitations could be first extended to women who were under surveillance because they had a positive test but an insufficient risk to merit colposcopy before the start of the pandemic. Alternatively, prioritisation could be made on the basis of the recorded screening history, if personalised records included pathology results. If this information is not available, prioritisation could be made simply on the time since the previous test.

Many screening services, even those with robust screening databases, might find it difficult to identify and prioritise patients by risk profile. In that case, the most straightforward way to deliver a risk-based recovery strategy could be to prioritise by age. In most settings, information on age is readily available at the point of care. A modelling study of COVID-19-related delays in Australia found that an excess of cervical cancer diagnoses will be most frequent among women aged 30–49 years,³² consistent with the age range at which most countries with screening programmes observe peak cervical cancer incidence.³³ Furthermore, targeting underscreened women who surpassed the upper age of screening for a so-called exit test (usually aged 60–65 years) because of COVID-19-related delays might provide important gains in mitigating the excess cancer burden.^{34,35}

	Principles	Advantages	Disadvantages
Risk-based triage			
Age	Deprioritise women in age groups in which risk of cancer from missed screens is low	Age can be identified at point of care or from screening registry; administratively simple	Age-based stratification might be a crude prioritisation tool for older women (aged 50–70 years) at elevated risk
Previous screen history	Deprioritise women with a previous negative test by extending the interval between screening tests	Capacity targeted to women whose most recent test was positive and who are under surveillance	Risks associated with interval extensions will depend on the primary screening modality, test sensitivity achieved, programme intervals, and disease incidence; screening history might be difficult to ascertain in settings without screening registries
HPV vaccination status	Deprioritise women who are vaccinated against HPV	Enables risk stratification of well screened women	Difficult to ascertain in countries without screening or vaccination registries, or in countries where registries are not linked; the number of women eligible for deintensification might be low
Preservation of service			
Women with suspected high-grade or invasive disease on previous screen	Deprioritise colposcopy capacity for individuals referred with suspected low-grade abnormalities or for women who are HPV-positive to types other than 16 and 18 without high-grade cytology	Degree of risk (high) ascertained	Colposcopy services might be slower to recover than primary screening; requires the capacity to identify and actively invite those women who test positive at screening for further assessment or strong provider-level follow-up protocols
Medical history	Prioritise immune-suppressed women	Can be established at point of care	Might be more difficult to ascertain in non-primary care-based health systems
Awareness campaigns			
Age	Target awareness campaign by age group	Enables effective media buying and development of material for promotional campaigns	Engaging women in the recovery phase will be challenging and will probably require thoughtful communication strategies
Geographical location	Target awareness campaign to women in areas of high deprivation	Can be identified by postcode; enables effective media buying and development of material for promotional campaigns	Might miss particular ethnic groups with high economic status but low participation in screening
Screening innovations			
HPV self-sampling	Offer HPV self-sampling instead of in-clinic appointments to all women or to women in high-risk categories	Can overcome socioeconomic and COVID-19-related barriers to screen; can allow women in the shielding category to safely screen at home	Regulatory approval not yet in place in some countries; there might be insufficient laboratory capacity for additional preanalytical processes and shortage of reagents and consumables
Strategies are not exclusive of each other. HPV=human papillomavirus.			
Table: Potential recovery strategies for resuming routine cervical screening during the COVID-19 pandemic and their differing advantages and disadvantages			

Targeting by age group also enables effective media buying and development of material for promotional campaigns, which could be used to supplement, or as an alternative to, personal invitations (eg, as used in Australia).³⁶ Another option is to target women in geographical areas known to have low screening participation and high levels of deprivation through tailored awareness campaigns.

If information on vaccination is available to screening programmes, recovery should further prioritise screening of non-vaccinated women younger than 50 years, given that the difference in the risk of cervical cancer between vaccinated and unvaccinated cohorts is so large.^{37,38} Offering vaccination to women aged 26 years and older is not recommended because it is likely to have a marginal benefit in terms of cancer prevention and represents poor value for money.^{39,40}

A negative screening test does not prevent cervical cancer; instead, it indicates a low risk of it developing in the near future. The risk of cervical cancer following a negative test increases with time since the most recent test; therefore, screening needs to be repeated at regular intervals.^{41,42} Nevertheless, when trade-offs need to be made during the recovery period, a small extension in the screening interval for previously well screened women will have a small impact on their risk of cervical cancer compared with what could be achieved by increasing participation among women who have been underscreened for longer.⁴³ A temporary relaxation of the screening frequency to prioritise life-long coverage in a screening service with constrained capacity will mitigate the impact among women who are underscreened.⁴⁴

The risks associated with a (temporary) extension of the screening interval are inversely related to screening test sensitivity. Because the negative predictive value of a HPV test is higher than that of cytology,^{21,37,45} extending the interval from 5 years to 6 years for women who had a recent negative HPV test will carry a lower excess risk of cervical cancer than will extending a typical interval of 3 years to 4 years after a negative test in a cytology-based programme.²⁰ From this perspective, settings in which women had a HPV test as their most recent screening test will be more resilient to the delays caused by COVID-19. However, settings in which HPV screening intervals are set at more than 5 years⁴⁶ might find that they are less able to absorb a deintensification of screening for women screened as recommended, particularly when compared with HPV-based programmes that recommend relatively intensive screening with an early starting age and short intervals (<5 years).⁴⁷

The effects of small extensions to screening intervals will vary between settings, depending on factors including the testing technology used, test performance achieved, programme intervals, and disease incidence. Decision makers responsible for screening policy will need to interpret the benefits of interval extension within their local context.

For cancer screening to achieve its goal, screen-detected abnormalities must be appropriately followed up.⁴⁸ Cervical cytology results of severe dyskaryosis (equivalent to high-grade squamous intraepithelial lesions) or worse have a sensitivity of 78.1% and a positive predictive value of 5.3% to detect prevalent cervical cancer.⁴⁹ Therefore, when colposcopy capacity is constrained, there is a need to prioritise appointments by the outcome of the screening test result to ensure that individuals with suspected cancer are seen as soon as possible (eg, within 4 weeks), followed by those with high-grade abnormal primary screening tests (eg, within 1–3 months). By contrast, appointments for women with low-grade abnormalities can be delayed for longer (eg, up to 6–12 months).³¹

The deployment of HPV-self sampling⁵⁰ might provide an effective recovery strategy to increase the number of women to whom screening is offered during or following disruptions to screening, while minimising the demands on the capacity needed to take screening samples. Self-sampling might increase screening participation in underscreened women or among women who have missed appointments due to fears of being exposed to SARS-CoV-2 in transit to, or at, their local health-care facility. In the Netherlands, the availability of self-sampling as an alternative to booking a clinician appointment has been highlighted in invitation letters since November, 2020. Preliminary information suggests that the number of screening self-samples received at laboratories has doubled and overall screening participation has largely recovered, even though the number of clinician-taken tests remains low (van Dijk S, Centre for Population Screening, Dutch National Institute for Public Health and the Environment, personal communication).

Several points related to self-sampling require consideration. HPV testing competes for reagents used for testing COVID-19. Although evidence suggests that the sensitivity of PCR-based tests on self-collected samples is consistent across various self-sampling devices,³¹ in some countries, the available self-sampling devices have not yet been formally approved for use in cervical screening. Furthermore, few (if any) preanalytical laboratory protocols for self-sampling devices are automated (eg, dry swabs need to be resuspended). Few device or assay combinations are designed for medium-to-high throughput testing, meaning that their processing is more labour-intensive and time-consuming than is the processing of clinician-taken samples.⁵² Thus, even in programmes that have already switched to HPV testing, a large-scale roll-out of self-sampling would require infrastructure that most programmes do not have readily available. Additionally, triage is required for women who are HPV-positive, and, at present, there are no clinically validated molecular biomarkers that could expedite triage on a self-sample. Women with positive self-samples will usually be recommended

to have a sample taken in primary care so that it can be processed for cytology reading because cytology assessment cannot be done directly from the self-sample. These caveats suggest that self-sampling might not be a realistic strategy to rapidly scale up during this pandemic; however, it is certainly a promising option for the future.⁵²

An important caveat to the COVID-19 responses considered here is that they are considered in a high-income country context. Low-income and middle-income countries typically do not have the advantage of high-quality, population-wide cervical screening programmes supported by screening databases. Accordingly, where population screening does exist, the challenges are likely to be all the greater. Nevertheless, the broad principles of the strategies outlined in this Viewpoint will still apply—namely, targeting scarce capacity at individuals in greatest need and prioritising coverage over intensity.

In time, research will be required on what policy choices decision makers in charge of cervical screening ultimately take and what the consequences are for processes and health outcomes. This work will need to consider the relevance of context and the distributional consequences of policy responses. We hope that the considerations outlined in this Viewpoint might help to inform such research.

Conclusion

Risk-based strategies appear to be the most effective way for screening services to recover following disruptions related to the COVID-19 pandemic. Although the degree to which screening is organised will determine the feasibility of deploying some of the strategies proposed in this Viewpoint, the implementation of an age-based risk stratification should be universally feasible. We caution against performance measures that rely solely on restoring testing volumes to pre-pandemic levels because they will be less effective at mitigating excess cancer diagnoses than will targeted measures. In addition, these measures might well exacerbate pre-existing inequalities in accessing cervical screening by disregarding the risk profile of individuals attending. Our group is actively working to provide policy makers with more specific evidence for recovery strategies.

Contributors

AC, MR, EAB, IMCMdK, MAS, SJBH, and JFOM conceptualised this Viewpoint. AC was responsible for project administration and wrote the original draft. MR, EAB, IMCMdK, MAS, SJBH, FMC, SP, and JFOM wrote, reviewed, and edited subsequent versions of the manuscript. All authors approved the final manuscript and were responsible for the decision to submit for publication.

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