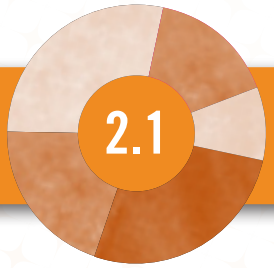
World Health Organization



PREVENTING HIV THROUGH SAFE VOLUNTARY MEDICAL MALE CIRCUMCISION FOR ADOLESCENT BOYS AND MEN IN GENERALIZED HIV EPIDEMICS

WEB ANNEX 2.1

GRADE AND EVIDENCE-TO-DECISION TABLES ON VOLUNTARY MEDICAL MALE CIRCUMCISION FOR HIV PREVENTION AMONG ADOLESCENTS AND MEN

Preventing HIV through safe voluntary medical male circumcision for adolescent boys and men in generalized HIV epidemics: recommendations and key considerations. Web Annex 2.1. GRADE and evidence-to-decision tables on voluntary medical male circumcision for HIV prevention among adolescents and men

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This publication forms part of the WHO guideline entitled *Preventing HIV through safe voluntary medical male circumcision for adolescent boys and men in generalized HIV epidemics: recommendations and key considerations*. It is being made publicly available for transparency purposes and information, in accordance with the *WHO handbook for guideline development*, 2nd edition (2014).

WEB ANNEX 2.1
GRADE AND EVIDENCE-TO-DECISION TABLES ON VOLUNTARY MEDICAL MALE CIRCUMCISION FOR HIV PREVENTION AMONG ADOLESCENTS AND MEN

Contents

Table A2.1.1. GRADE evidence profile: PICO question. Does male circumcision reduce the risk of infection in men exposed to HIV through heterosexual intercourse?

Author(s): Tim Farley

Date: 2019

Question: Does male circumcision reduce the risk of infection in men exposed to HIV through heterosexual intercourse?

Settings: High HIV incidence settings

Quality assessment							No. of patients [a]		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Circumcision	Control	Relative (95% CI) [b]	Absolute (95% CI) [c]		
Outcome: efficacy (incident HIV infection)												
3 [1-3]	randomized controlled trials (RCT)	some risk of bias [d]	no serious inconsistency	no serious indirectness	no imprecision	some concerns [e]	64/7791 p-y (0.82 per 100 p-y)	141/7945 (1.77 per 100 p-y)	IRR 0.41 (0.30 to 0.56)	10 fewer per 1000 p-y (from 8 to 12 fewer)	●●●● HIGH	CRITICAL
2 [4,5]	post-RCT follow-up studies	some risk of bias [f]	no serious inconsistency	no serious indirectness	no imprecision	none	95/15 372 p-y (0.62 per 100 p-y)	100/5194 p-y (1.93 per 100 p-y)	aIRR 0.34 (0.24 to 0.49)	13 fewer per 1000 p-y (from 10 to 15 fewer)	●●●● HIGH	CRITICAL
5 [6-10]	cohort studies of men at high HIV risk	some risk of bias [g]	some inconsistency [h]	no serious indirectness	no imprecision	none	60/3444 p-y (1.7 per 100 p-y)	258/4756 p-y (5.4 per 100 p-y)	aIRR 0.29 (0.19 to 0.43)	39 fewer per 1000 p-y (from 31 to 44 fewer)	●●●● HIGH	CRITICAL
4 [7,11-13]	population-based cohort studies before circumcision scale-up	some risk of bias [i]	no serious inconsistency	no serious indirectness	no imprecision	some concerns [j]	58/9466 [k] p-y (0.61 per 100 p-y)	171/9930 [k] p-y (1.72 per 100 p-y)	aIRR 0.48 (0.33 to 0.70)	9 fewer per 1000 p-y (from 5 to 12 fewer)	●●●● HIGH	CRITICAL
6 [14-19]	population-based cohort studies during circumcision scale-up	some risk of bias [l]	no serious inconsistency	no serious indirectness	no imprecision	none	216/28 233 [m] p-y (0.77 per 100 p-y)	953/61 553 [m] p-y (1.55 per 100 p-y)	aIRR 0.56 (0.49 to 0.64)	7 fewer per 1000 p-y (from 6 to 8 fewer)	●●●● HIGH	CRITICAL

Table A2.1.1. (continued)

Quality assessment							No. of patients [a]		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Circumcision	Control	Relative (95% CI) [b]	Absolute (95% CI) [c]		
Outcome: efficacy (prevalent HIV infection in communities with recent circumcision scale up)												
2 [16,19]	community-based studies	some risk of bias [n]	some inconsistency [o]	no serious indirectness	no imprecision	none	1485/7306 (203 per 1000)	2487/6910 (360 per 1000)	aPR 0.65 (0.60 to 0.70)	148 fewer per 1000 (from 134 to 162 fewer)	●●●○ MODERATE	IMPORTANT

Notes

[a] Number of HIV infections/person-years exposure (p-y).
[b] Pooled incidence rate ratio (IRR) from study-specific IRRs (adjusted IRR [aIRR] for observational studies) or pooled adjusted prevalence ratio (aPR) with weights inversely proportional to variance.
[c] Estimated from pooled IRR or aIRR and incidence in control arm or among uncircumcised men pooled over all studies in subgroup.
[d] Potential bias due to impossibility of blinding participants to intervention or control.
[e] All three RCTs stopped early due to strong protective effect. Effect size may be exaggerated.
[f] Potential bias due to self-selection to circumcision following closure of RCTs and dissemination of study results. Adjustment for likely confounders had little impact on risk estimates, but residual confounding cannot be excluded.
[g] Potential bias due to unmeasured confounding, self-reported circumcision status (one study).
[h] Some heterogeneity in magnitude of effect, reflecting diversity of high-risk populations.
[i] Potential bias due to unmeasured confounding, self-reported circumcision status, inadequate adjustment for potential confounding factors (one study), long interval between baseline and follow-up surveys (one study).
[j] HIV incidence estimated from cross-sectional assay rather than repeat serology (one study).
[k] Number of HIV infections and person-years from three African studies only.
[l] Potential bias due to unmeasured confounding, self-reported circumcision status (four studies), failure to account for men circumcised during follow-up period and inadequate adjustment for potential confounders (one study).
[m] Excluding one study for which no information available.[16]
[n] Potential bias due to unmeasured confounding, self-reported circumcision status (one study).
[o] Some heterogeneity in magnitude of effect.

Table A2.1.2. GRADE evidence profile: PICO question. Does male circumcision reduce the risk of infection in women exposed to HIV through heterosexual intercourse?

Author(s): Tim Farley

Date: 2019

Question: Does male circumcision reduce the risk of infection in women exposed to HIV through heterosexual intercourse?

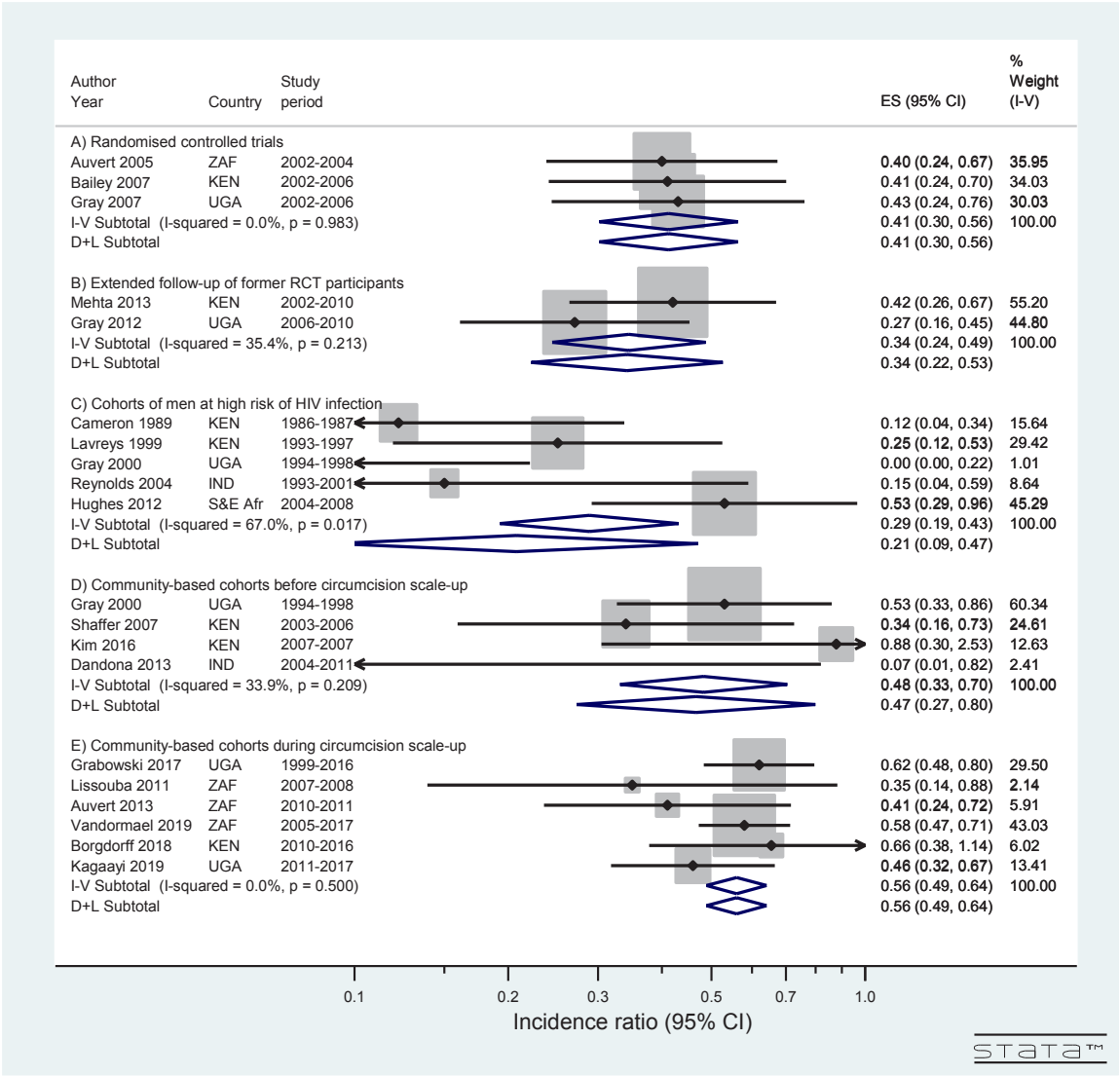
Settings: High HIV incidence settings

Quality assessment							No. of patients [a]		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Circumcision	Control	Relative (95% CI) [b]	Absolute (95% CI) [c]		
Outcome: risk of HIV infection in women (secondary, indirect benefit to women)												
1 [20]	randomized controlled trial in HIV-infected men	serious risk of bias [d]	no serious inconsistency	no serious indirectness	serious imprecision [e]	none	17/148 p-y (11.5 per 100 p-y)	8/115 p-y (6.9 per 100 p-y)	IRR 1.49 (0.62 to 3.57)	34 more per 1000 p-y (from 26 fewer to 178 more)	●○○○ VERY LOW	CRITICAL
2 [7,21]	cohort studies of serodiscordant couples	some risk of bias [f]	no serious inconsistency	no serious indirectness	some imprecision [e]	none	19/646 p-y (2.94 per 100 p-y)	94/1445 p-y (6.51 per 100 p-y)	IRR 0.59 (0.35 to 0.99)	27 fewer per 1000 p-y (from 0 to 27 fewer)	●●○○ LOW	CRITICAL
4 [18,22-24]	cohort studies of women with partners' HIV status undocumented or mixed	moderate risk of bias [g]	no inconsistency	no indirectness	some imprecision [e]	none	97/7412 p-y (1.31 per 100 p-y)	311/21 678 p-y (1.43 per 100 p-y)	IRR 0.75 (0.56 to 1.00)	4 fewer per 1000 p-y (from 0 to 6 fewer)	●●○○ LOW	CRITICAL

Notes

[a] Number of HIV infections/person-years exposure (p-y).
[b] Pooled incidence rate ratio (IRR) from study-specific IRRs with weights inversely proportional to variance.
[c] Estimated from pooled IRR and incidence in control arm or among uncircumcised men pooled over all studies in subgroup.
[d] Serious risk of bias due to HIV-infected men randomized to circumcision or control arms but outcome assessed in subset with documented HIV-negative consenting female partners (17% of originally randomized cohort). Some risk of bias due to impossibility of blinding participants to group allocation.
[e] Small number of incident HIV infections and wide confidence intervals.
[f] Potential bias due to unmeasured confounding, self-reported circumcision status (one study).
[g] Potential bias due to unmeasured confounding, partner's circumcision status reported by woman, failure to account for changes in circumcision status during follow-up (two studies).

Fig. A2.1.1. Impact of voluntary medical male circumcision on HIV incidence in heterosexual men



BWA = Botswana, IND = India, KEN = Kenya, UGA = Uganda, ZAF = South Africa, S&E Afr = seven countries in East and Southern Africa (BWA, KEN, RWA = Rwanda, TZA = United Republic of Tanzania, UGA, ZAF, ZMB = Zambia)

Source: Farley TMM, Samuelson J, Grabowski MK, Ameyan W, Gray RH, Baggaley R. Impact of male circumcision on risk of HIV infection in men in a changing epidemic context – systematic review and meta-analysis. J Int AIDS Soc. 2020;23(6):e25490.

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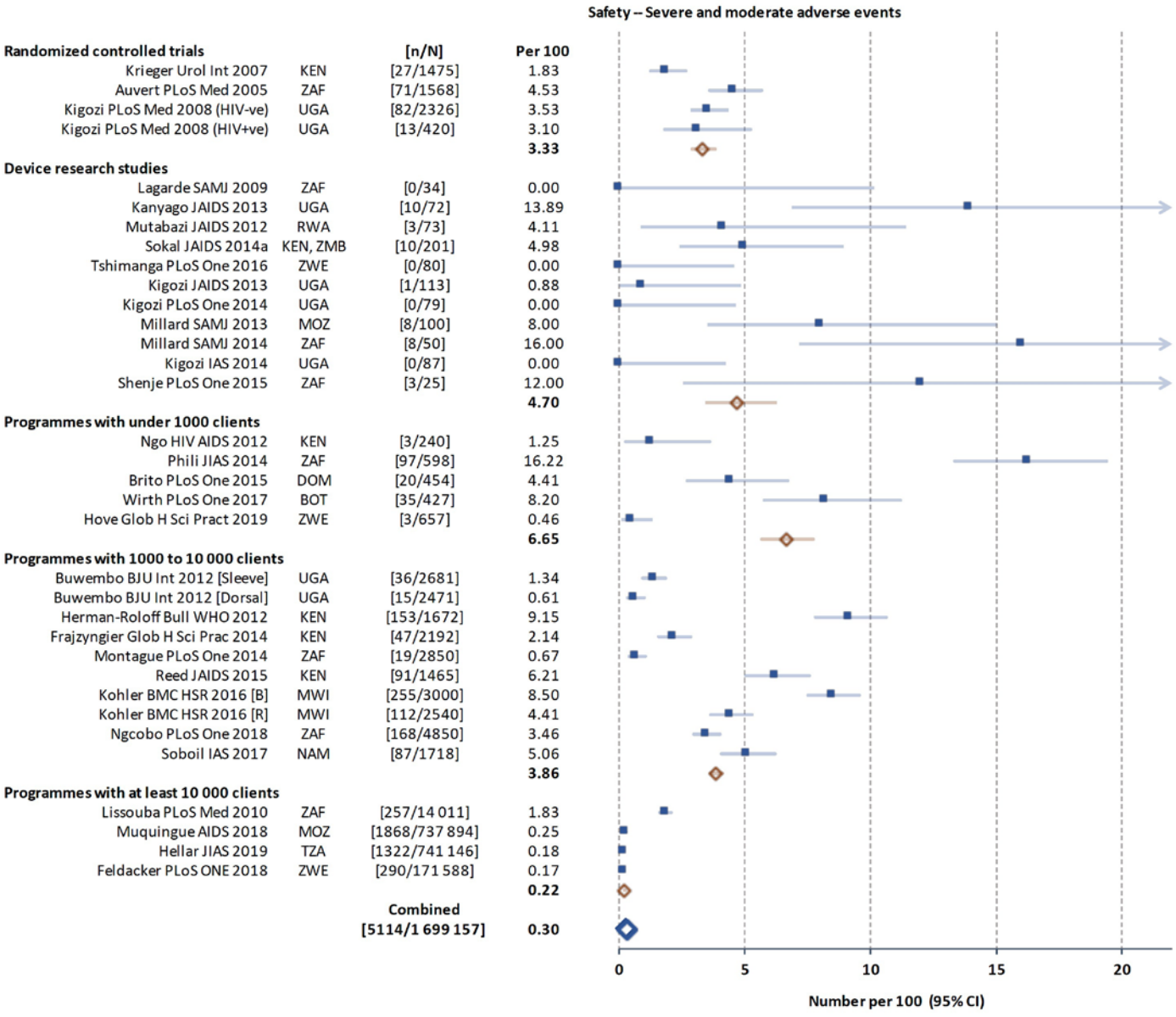
Fig. A2.1.2. Rates of severe and moderate adverse events in studies of voluntary medical male circumcision for adolescents and men

■ Point estimate ◇ Pooled estimate ◇ Combined point estimate for all studies



BOT = Botswana; DOM = Dominican Republic; KEN = Kenya; MOZ = Mozambique; MWI = Malawi; NAM = Namibia; RWA = Rwanda, TZA = United Republic of Tanzania, UGA = Uganda; ZAF = South Africa; ZMB = Zambia; ZWE = Zimbabwe.

Source: Jindai K, Awori Q, Farley T, Temu J, Samuelson J. Safety of male circumcision for HIV prevention by conventional surgical methods and age, unpublished; available from WHO/UCN/Global HIV, Hepatitis and STIs Programmes (hiv-aids@who.int).

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Table A2.1.3. GRADE evidence profile: PICO question. Among adolescents under 15 years, compared with older adolescent boys or men, is surgical male circumcision safe?

Author(s): Tim Farley

Date: 2019

Question: Among adolescents under 15 years, compared with older adolescent boys or men, is surgical male circumcision safe?

Settings: Voluntary medical male circumcision programmes for HIV prevention

Quality assessment							No. of patients (no. of events/no. at risk)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Age <15 yr	Age ≥15 y	Relative (95% CI) [h]	Absolute (95% CI) [i]		
Outcome: moderate or severe adverse events (all types)												
0	MCs performed in randomized trials of circumcision for HIV prevention [a]	—	—	—	—	—	—	—	—	—		CRITICAL
1 [1]	surgical circumcision arm of MC device comparative studies [b]	—	—	—	—	—	0/127 (0.0%) b	—	—	—		CRITICAL
3 [2-4]	VMMC programmes with 1000 – 10 000 clients	serious risk [c]	some inconsistency [d]	some indirectness e	serious imprecision [f]	none	15/755 (1.9 per 100)	181/4597 (3.9 per 100)	0.80 (0.48,1.35)	14 fewer per 1000 (from 6 to 22 fewer)	●○○○ VERY LOW	CRITICAL
2 [5,6]	VMMC programmes with at least 10 000 clients	some risk [g]	no inconsistency	no indirectness	no imprecision	none	811/407 944 (0.20 per 100)	1213/374 778 (0.32 per 100)	0.62 (0.57, 0.68)	1.2 fewer per 1000 (from 1.0 to 1.5 fewer)	●●○○ LOW	CRITICAL
Outcome: moderate or severe adverse events – infections												
1 [6]	VMMC programmes with at least 10 000 clients	some risk [g]	—	no indirectness	no imprecision	none	47/19 619 (0.24 per 100)	27/25 249 (0.32 per 100)	2.24 (1.40, 3.60)	1.3 more per 1000 (from 0.5 to 1.2 more)	●●○○ LOW	CRITICAL

Notes

[a] Age ranges 18-24 years, 17–28 years and 15-49 years in the three RCTs.
[b] Age range 13–17 years, no AEs in surgical MC group. Breakdown of circumcisions by age group not given.
[c] One study in Kenya with clinical follow-up visit conducted in client's home if scheduled 1 week post circumcision clinic follow-up visit missed found an additional 52 AEs beyond the 23 AEs identified at clinic visit. Under-ascertainment of AEs markedly greater in clients age 13–17 years compared with those age 18 years and older.
[d] Overall AE rates varied considerably between studies.
[e] Target comparison between ages 10–14 years and ≥ 15 years – two studies compared age groups 13–17 years with ≥ 18 years, one study compared age groups 15–19 years with ≥ 20 years.
[f] Small number of events and few clients age under 15 years.
[g] Reported AE rate 10-fold lower than in smaller VMMC programmes with facilities for better monitoring.

References for Table A2.1.3

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Table A2.1.4. Evidence-to-decision-making: male circumcision for HIV prevention

Recommendation: Voluntary medical male circumcision (VMMC) should continue to be promoted as an additional efficacious HIV prevention option within combination prevention for adolescent boys 15 years and older and for adult men in settings with generalized epidemics to reduce the risk of heterosexually acquired HIV infection.

Factor	Explanation/evidence	Judgment
Quality of evidence	High quality, consistent evidence over diverse range of study types including three randomized controlled trials	Strong
Balance of benefits versus harms	**Preventing heterosexually acquired HIV infection** • Efficacy is partial but consistent and lifelong. • Impact in communities was noted, including alongside scale-up of antiretroviral treatment (ART). • VMMC intervention remains necessary to achieve epidemic control even in the context of other current efficacious prevention intervention options and ART scale-up in East and Southern Africa. • Impact among women is indirect, with possible direct effect after wound healing. **Other benefits** • Circumcised men and their female partners experience lower rates of several sexually transmitted infections, including human papillomavirus, herpes simplex virus type 2, bacterial vaginosis and Trichomonas vaginalis, than uncircumcised men and their female partners. • Women benefit indirectly, from the lower risk of HIV infection in circumcised men as VMMC programmes expand and fewer men acquire HIV. • Women may be somewhat less likely to acquire HIV infection from an HIV-positive man who is circumcised than from one who is not. **Other issues addressed** • Traditional male circumcision may be undertaken in collaboration with the formal health sector providing the surgical procedure, thus reducing risk with traditional circumcision methods. **Harms** • Severe and moderate adverse events and rates were reportedly low, but adverse events do occur, which requires that clients understand risks and benefits. • No evidence noted of increases in risky sexual behaviours (risk compensation), including less condom use or more partners, but education on safer sexual behaviour is essential with provision of VMMC. • If a man who has HIV wants circumcision, he should be on ART prior to undergoing circumcision, both for his own health and to reduce his HIV viral load and, thus, transmission risk during the healing period.	In high HIV burden settings, particularly East and Southern Africa, benefits greatly outweigh harm.
Values and preferences	• HIV prevention and risk reduction: valued by programmes in high burden countries and donors for its contribution to preventing HIV and associated burden and its potential to reach men for other health care interventions such as screening and treatment for noncommunicable diseases. • Limited information on values of preventing HIV from the perspective of men and women; some information on older men in East and Southern Africa indicated that higher priority concerns are livelihood, food, sex. • One qualitative process evaluation of a sports-based intervention noted that older men (over 30 years) reported a lack of motivation for circumcision because HIV testing and VMMC would make little difference at their age.	Due to limited evidence, it is not possible to assess if there are any important uncertainties and variabilities in the importance of VMMC for HIV prevention. The Guideline Development Group considered the health burden of HIV, including its social implications, to be large. It is important to implement effective interventions that help people to avoid this burden.
Resource use	VMMC is cost-effective and in many settings cost-saving within the next 5–10 years.	Strongly in favour
Equity and human rights	• A few studies were identified that address equity. Traditional community values are a key factor directly affecting the acceptability of VMMC, thus indirectly affecting equity. Those who live in communities where VMMC is not supported have been adversely affected in terms of equity. In one study in Tanzania, people who resided in remote locations, farther than 5 km and, even more so, farther than 10 km from a fixed VMMC facility, were likely to be disadvantaged for post-VMMC follow-up. • As a one-time intervention, reduction in risk will continue over a lifetime. • VMMC must be provided in line with human rights, ethical and legal considerations, including high quality information for communities, women and men; informed voluntary consent; and high quality, safe services that are monitored for adverse outcomes. • VMMC should be provided only as part of a combination prevention package.	Equity favours the one-time intervention to permanently reduce heterosexual HIV risk in men. Ethics and human rights are essential. The overall ethical justification for VMMC as a public health initiative is dynamic and depends on a number of different factors that can change over time, including the emergence of new HIV prevention modalities, epidemiological changes, new data about safety and new approaches to voluntary informed consent.
Feasibility	• Scaling up to 23 million men circumcised between 2008 and 2018 demonstrates feasibility in many settings. – This scale-up occurred mostly using a vertical approach with donor support. However, integrated approaches showed positive outcomes towards sustaining services. – Challenges and barriers faced in scaling up are specific to context and population. – Global efforts now underway to scale up adolescent services and essential and emergency surgical services present opportunities for synergies.	The Guideline Development Group considered VMMC a feasible intervention and favoured a recommendation recognizing the need for sufficient resource capacity.

Table A2.1.4. (continued)

Factor	Explanation/evidence	Judgment
Acceptability of VMMC intervention	**Men, women, community leaders, programmes, policy** • To date over 23 million VMMCs have been performed, demonstrating acceptability. • Age disaggregation demonstrated higher acceptability among adolescents and lower acceptability among older men, although evidence on adolescent or parental acceptability was limited. • Regional and cultural differences in acceptability. • Main drivers of acceptability were reduction in risk of HIV and STIs and improved hygiene.	VMMC considered acceptable in high HIV burden settings, with recognition of variation by age and culture.

Table A2.1.5. Evidence-to-decision-making: offer of VMMC to younger adolescent boys (ages 10–14 years)

Factor	Explanation/evidence	Judgment
Balance of benefits versus harms	Benefits of lifetime HIV and STI prevention versus harms of potentially higher frequency of severe adverse events (SAE), including some rare events with possible long-term consequences, in the younger age adolescent boys (10–14 years) were the main factors considered. These considerations are based on limited evidence of SAE risk and uncertainties about future HIV incidence. **Benefits.** Biological effectiveness of VMMC in reducing heterosexually acquired HIV is expected to be the same for younger adolescents as among those circumcised above age 15 years ("older adolescents"). Risk of other STIs also reduced. Less risk of HIV acquisition during healing period in younger adolescents, as they are less likely to be sexually active. Faster healing among younger adolescents than among older adolescents. **Harms.** The frequency of glans injuries was greater among younger adolescents (particularly those whose genitalia were less mature) compared with adolescents 15 years and older; however, some uncertainty exists regarding the magnitude of excess risk based on adverse event data available. All reported cases of glans injury and 98% of urethral fistula cases occurred among those under 15 years. Uncertainty exists regarding the potential harms of bullying/stigmatization when circumcision in a younger adolescent is deferred until more physically mature. **Other.** May be advantageous to provide VMMC services package to adolescents at a later developmental stage, when they can better understand HIV prevention and sexual and reproductive health (SRH) information and education. Overall, need to improve safety monitoring, including disaggregation by narrower age bands and by stage of sexual maturity.	Uncertainty regarding balance between benefits compared with possible harms. Better safety data are needed. Age is used as a proxy for physical maturity. But the age when adolescents reach physical maturity varies. Therefore, some flexibility is needed rather than deciding by age alone. The offer of VMMC to younger adolescents depends on their capacity to provide fully informed consent.
Values and preferences	No evidence from literature on relative values and preferences for safety or on maintaining VMMC coverage for a particular age group of adolescents. The Guidelines Development Group noted: • the importance of HIV as a public health burden; thus, there is a need to maintain high coverage. • Some adolescents are sexually active before the age of 15 years.	No judgment possible
Acceptability of male circumcision at younger adolescent ages	Evidence on acceptability by boys and parents comes only from limited studies, which consistently show high acceptability by parents/mothers and fathers for circumcision of sons, including at younger adolescent ages (<14 years). Social norms have changed in East and Southern Africa since the initial 2007 recommendation, with programmatic evidence suggesting that VMMC for this age group is acceptable. About 45% of the VMMCs since 2015 have been for adolescents ages 10–14. Community context must be considered also. Some health care providers noted that it is not possible to provide meaningful SRH education to younger adolescents. Several barriers and facilitators to implementing VMMC for younger adolescent were reported, with pain the most commonly mentioned barrier to acceptability and HIV protection the most commonly cited facilitator. Convenient timing (for example, after school terms) increases acceptability. Although the Guidelines Development Group favoured prioritization of VMMC for adolescents whose genitalia are mature, evidence overall suggests that VMMC may be acceptable for younger adolescent boys and their parents if concerns about pain and peri- and post-procedural care are weighed against the benefits of HIV prevention. If a national programme decides to include younger adolescents, it must put in place the necessary precautions to ensure the safety of those adolescents not yet physically mature and/or not yet having the capacity to consent.	VMMC for younger adolescents seems acceptable, but limited evidence is available for this age group.
Resource use	Conclusions from two references: • VMMC is a one-time intervention that results in lifelong benefits for the individual and community. • Most males ages 10–14 years are not sexually active. Thus, there is a time lapse before they benefit from VMMC. Although cost-effectiveness modelling suggests that VMMC in boys ages 10–14 years may not be a programme priority, turning them away would mean refusing services to some (varies by country) clients accessing VMMC services and could be viewed by implementers as a likely missed opportunity, given less demand for VMMC to date among older males. Inclusion of other services has not been assessed in terms of efficiencies or effectiveness, but the opportunity to provide other recommended services, such as tetanus toxoid-containing vaccination booster, prevention education and other locally relevant interventions could increase cost-effectiveness and impact.	Resource use is uncertain, as multiple factors not taken into account beyond the cost of VMMCs per HIV infection averted.

Table A2.1.5. (continued)

Factor	Explanation/evidence	Judgment
Equity and ethics	• No evidence from the literature • Age of consent for surgical procedures varies by country. • International human rights standards encourage postponing a non-emergency, invasive and irreversible procedure until the adolescent is sufficiently mature to provide his informed consent. Evolving capacity has a bearing on independent decision-making, such that some younger adolescents may be able to provide consent. • If national programmes offer VMMC to younger adolescents who do not yet have the capacity to consent, assent from minors should be obtained as well as parental/guardian consent that is provided on the day of surgery.	A human rights-based approach calls for a fair opportunity to access VMMC services. Ethics calls for ensuring consent or, if offered to a minor, assent along with consent of parent/guardian.
Feasibility	• ≈50% of VMMCs have been performed in adolescents <19 years, with a varying percentage among 10–14 year olds. • As this age group is seeking health care services, guidance is needed on how to manage the younger adolescents and their parents when VMMC is not offered. Need to consider providing other services and follow-up to support clients returning later for VMMC. • Evidence points to the need for improvements in provider training and better counselling of younger males and for adolescent-specific counselling guidelines (for example, on condom use and on HIV counselling in general and specific to disclosing HIV-positive test results to younger clients). • Tools to assess physical maturity are not readily available, and health care workers would need adequate training to correctly assess physical maturity. (Physical maturity is not equivalent to cognitive maturity or capacity to consent.) • Need to address issues regarding timing (vis-à-vis school and exams) and to engage with parents. • VMMC is an important opportunity to provide adolescent boys with information and counselling on SRH issues, but HIV testing services may not be needed for the youngest clients.	Although providing VMMC to younger adolescents is feasible (as evidenced by the experience to date of programmes, which have provided VMMC to a large number of younger adolescents), there are uncertainties regarding the feasibility of how to deliver VMMC and other services to younger adolescent boys and providers' capacity to assess their physical and cognitive capacity.

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