Surgical site infections 1

New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective

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Surgical site infections (SSIs) are among the most preventable health-care-associated infections and are a substantial burden to health-care systems and service payers worldwide in terms of patient morbidity, mortality, and additional costs. SSI prevention is complex and requires the integration of a range of measures before, during, and after surgery. No international guidelines are available and inconsistencies in the interpretation of evidence and recommendations of national guidelines have been identified. Given the burden of SSIs worldwide, the numerous gaps in evidence-based guidance, and the need for standardisation and a global approach, WHO decided to prioritise the development of evidence-based recommendations for the prevention of SSIs. The guidelines take into account the balance between benefits and harms, the evidence quality, cost and resource use implications, and patient values and preferences. On the basis of systematic literature reviews and expert consensus, we present 13 recommendations on preoperative preventive measures.

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This is the first in a Series of two papers about surgical site infections

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Introduction

Health-care-associated infections are avoidable infections that affect hundreds of millions of people each year worldwide. Following a systematic review of the literature and meta-analyses, WHO reported in 2010 that the prevalence of health-care-associated infections in low-income and middle-income countries (LMICs) was two to 20 times higher than in high-income countries.[1–3] Surgical site infection (SSI) was the most surveyed and most frequent health-care-associated infection in LMICs, affecting up to a third of patients who had surgery. The incidence of SSI is much lower in high-income countries, but it is still the second most common cause of health-care-associated infection in Europe and the USA.[1,4] Furthermore, data from the USA showed that up to 60% of the microorganisms isolated from infected surgical wounds have antibiotic resistance patterns.[5]

Considering the epidemiological importance of SSIs, and the fact that these infections are largely preventable, WHO decided to prioritise the development of evidence-based recommendations for the prevention of SSIs. Many factors in the patient's journey through surgery contribute to the risk of SSI, and prevention is complex and requires the integration of a range of measures before, during, and after surgery. Further strong reasons to develop global guidelines on this topic include the absence of any international guidance document and inconsistencies in the interpretation of the evidence and strength of recommendations in national guidelines. We present the WHO recommendations for measures to be implemented or initiated during the preoperative period. These were elaborated according to the best available scientific evidence and expert consensus with the aim to ensure high-quality care for every patient, irrespective of the resources available. Important topics such as SSI surveillance are not mentioned in this Review because formal recommendations have not been made, but they are extensively reviewed in the WHO guidelines as cornerstones of SSI prevention. The intended audience for these recommendations is primarily the surgical team (ie, surgeons, nurses, technical support staff, anaesthetists, and any professionals directly providing surgical care), infection prevention and control professionals, policy-makers, senior managers, and hospital administrators. People responsible for staff education and training are also key stakeholders and implementers.

Methods

Data gathering

We developed the WHO guidelines following the standard methods described in the WHO handbook for guideline development.[6] We identified and formulated key research questions on priority topics for SSI prevention according to the Population, Intervention, Comparator, Outcomes process,[7] on the basis of expert opinion. SSI and SSI-attributable mortality were the primary outcomes for all research questions. We did targeted systematic literature reviews and reported the results according to the PRISMA guidelines.[8]

The quality of the studies was assessed using the Cochrane Collaboration tool to assess the risk of bias of randomised controlled trials (RCTs) and the Newcastle-Ottawa Quality Assessment Scale for cohort studies.[9,10] We did meta-analyses of available studies using Review Manager version 5.3, as appropriate. We pooled

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crude estimates as odds ratios (ORs) with 95% CIs using a random effects model, and used the Grading of Recommendations Assessment, Development, and Evaluation methods to assess the quality of the retrieved evidence.[11,12] We graded the quality of studies as high, moderate, low, or very low.

Data analysis and the development of recommendations

A guidelines development group was formed to assess the available evidence, develop recommendations, and decide on their strength on the basis of the balance between benefits and harms, the evidence quality, cost and resource use implications, and user and patient values and preferences. Members of the panel were key international experts selected by taking into account geographical distribution and gender balance, and ensuring representation from various professional groups, including surgeons, nurses, infection prevention and control professionals, infectious disease specialists, researchers, and patient representatives. They rated the strength of recommendations as either strong (the expert panel was confident that the benefits of the intervention outweighed the risks) or conditional (the panel considered that the benefits of the intervention probably outweighed the risks), on the basis of the quality of the evidence and an assessment of resource implications and feasibility, as well as patients' values and preferences. Strong recommendations are considered to be adaptable for implementation in most (if not all) situations, and patients should receive the intervention as the course of action. For conditional recommendations, a more structured decision-making process should be undertaken, on the basis of stakeholder consultation and the involvement of patients and health-care professionals. The recommendations and their individual strength, and the background research questions and remarks for implementation in LMICs are presented in the table.

Recommendation 1: perioperative discontinuation of immunosuppressive agents

The panel suggests not to discontinue immunosuppressive medication before surgery to prevent SSI (conditional recommendation, very low quality of evidence).

Immunosuppressive agents commonly used for preventing the rejection of transplanted organs or for the treatment of inflammatory diseases could lead to impaired wound healing and an increased risk of

	Key research question	Recommendations for prevention of SSIs	Strength of recommendation (quality of evidence retrieved†)	Notes for implementation in low-income and middle-income countries
(1) Perioperative discontinuation of immunosuppressive agents	Should immunosuppressive agents be discontinued perioperatively and does this affect the incidence of SSI?	Immunosuppressive medication should not be discontinued before surgery	Conditional recommendation (very low)	To be applied in patients on immunosuppressive medication only; not resource demanding
(2) Enhanced nutritional support	In surgical patients, should enhanced nutritional support be used for the prevention of SSIs?	Consider the administration of oral or enteral multiple nutrient-enhanced nutritional formulas in underweight patients who undergo major surgical operations	Conditional recommendation (very low)	Additional costs involved; need for pharmacy and dietician support; staff training; limited product availability
(3) Preoperative bathing	Is preoperative bathing using an antiseptic soap more effective in reducing the incidence of SSIs in surgical patients compared with bathing with plain soap; and are CHG-impregnated cloths more effective than bathing with antiseptic soap?‡	Patients should bathe or shower before surgery; either a plain soap or an antimicrobial soap may be used for this purpose	Conditional recommendation (moderate)	Availability of and access to clean water may be limited in rural areas; antimicrobial soap may be an additional cost for the health-care facility or patients
(4) Decolonisation with mupirocin ointment with or without CHG body wash in nasal carriers of *Staphylococcus aureus* undergoing cardiothoracic and orthopaedic surgery	Is mupirocin nasal ointment in combination with or without a CHG body wash effective in reducing the number of *S aureus* infections in nasal carriers undergoing cardiothoracic and orthopaedic surgery?	Patients with known nasal carriage of *S aureus* should receive perioperative intranasal applications of mupirocin 2% ointment with or without a combination of CHG body wash	Strong recommendation (moderate)	Evidence of cost-effectiveness in high-income countries; nasal mupirocin ointment availability is low and is an additional cost for the health-care facility or patients; requires technical laboratory capacity and extra resources for the screening process
(5) Decolonisation with mupirocin ointment with or without CHG bodywash in nasal carriers of *S aureus* undergoing other types of surgery	Is mupirocin nasal ointment in combination with or without a CHG bodywash effective in reducing the number of *S aureus* infections in nasal carriers undergoing other types of surgery?	Perioperative intranasal applications of mupirocin 2% ointment with or without a combination of CHG bodywash are suggested to be used also in patients undergoing other types of surgery	Conditional recommendation (moderate)	Nasal mupirocin ointment availability is low and is an additional cost for the health-care facility or patients; requires technical laboratory capacity and extra resources for the screening process
(6) MBP with the use of oral antibiotics	Is MBP combined with oral antibiotics effective for the prevention of SSI in colorectal surgery?	Preoperative oral antibiotics combined with MBP are suggested for use in adult patients undergoing elective colorectal surgery	Conditional recommendation (moderate)	It may require organisational resources for appropriate administration and possible additional costs; the oral antibiotics commonly used for MBP are inexpensive

(Table continues on next page)

	Key research question	Recommendations for prevention of SSIs	Strength of recommendation (quality of evidence retrieved†)	Notes for implementation in low-income and middle-income countries
(Continued from previous page)				
(7) MBP without the use of oral antibiotics	Is MBP without oral antibiotics effective for the prevention of SSI in colorectal surgery?	MBP alone (without the administration of oral antibiotics) should not be used in adult patients undergoing elective colorectal surgery	Strong recommendation (moderate)	It may require organisational resources for appropriate administration and possible additional costs; the oral antibiotics commonly used for MBP are inexpensive
(8) Hair removal	Does hair removal affect the incidence of SSI; and what method and timing of hair removal is associated with the reduction of SSI?§	In patients undergoing any surgical procedure, hair should either not be removed or, if absolutely necessary, it should be removed only with a clipper. Shaving is strongly discouraged at all times, whether preoperatively or in the operating room	Strong recommendation (moderate)	Clipper availability is low and their use is an additional cost for the health-care facility. If reused, appropriate cleaning and decontamination of clipper heads are crucial
(9) Optimal timing for administration of SAP	How does the timing of SAP administration affect the risk of SSI ?	Administration of SAP should be before the surgical incision when indicated	Strong recommendation (low)	Cost, feasibility, and equity were not identified as significant issues; however, organisational resources and staff training are needed for implementation
(10) Precise timing for administration of SAP	What is the precise optimal timing?	SAP should be administered within 120 min before incision, while considering the half-life of the antibiotic	Strong recommendation (moderate)	Cost, feasibility, and equity were not identified as significant issues; however, organisational resources and staff training are needed for implementation
(11) Surgical hand preparation	What is the most effective type of product for surgical hand preparation to prevent SSI; and what is the most effective technique and the ideal duration of surgical hand preparation?	Surgical hand preparation should be performed either by scrubbing with a suitable antimicrobial soap and water or using a suitable alcohol-based hand rub before donning sterile gloves	Strong recommendation (moderate)	Surgery should not take place without surgical hand preparation; evidence of alcohol-based hand rub cost-effectiveness exists, including in low-income and middle-income countries; however, availability of and access to clean water can be poor in rural areas; alcohol-based hand rub availability may also be limited and its use may represent an additional cost to the health-care facility; local production should be encouraged
(12) Surgical site preparation	In surgical patients, should alcohol-based antiseptic or aqueous solutions be used for skin preparation and, more specifically, should CHG or povidone-iodine solutions be used?	Alcohol-based antiseptic solutions based on CHG for surgical site skin preparation should be used in patients undergoing surgical procedures	Strong recommendation (low to moderate)	Availability of alcohol-based antiseptic solutions based on CHG is low and their use can be an additional cost for the health-care facility; local production should be encouraged
(13) Antimicrobial skin sealants	In surgical patients, should antimicrobial sealants (in addition to standard surgical site skin preparation) versus standard surgical site skin preparation be used for the prevention of SSI?	Antimicrobial sealants should not be used after surgical site skin preparation for the purpose of reducing SSI	Conditional recommendation (very low)	Avoidance of unnecessary costs

SSI=surgical site infection. CHG=chlorhexidine gluconate. MBP=mechanical bowel preparation. SAP=surgical antibiotic prophylaxis. *WHO recommendations for intraoperative and postoperative measures are included in paper 2[13] of this surgical site infections Series, to be read in combination with this Review. †The Grading of Recommendations Assessment, Development, and Evaluation method[11,12] was used to assess the quality of the retrieved evidence. ‡We decided not to formulate a recommendation for the use of CHG-impregnated cloths for the purpose of reducing SSI due to the scarce and very low quality evidence. §No recommendation regarding the timing of hair removal could be formulated because only one study assessed this question with no significant results, but we suggest that removal by clipping shortly before surgery is the safest approach, if required.

Table: **Summary of measures implemented or initiated during the preoperative period and related WHO recommendations for the prevention of SSIs***

infection in patients administered these agents.[14] By contrast, the discontinuation of immunosuppressive treatment could induce flares of disease activity, and long-term interruptions of therapy might induce the formation of anti-drug antibodies and subsequently decrease their effect.[15] We did a systematic review and meta-analyses to assess whether the discontinuation of immunosuppressive therapy in the perioperative period is effective to prevent SSIs in patients who undergo surgery.

We identified eight studies (one RCT,[16] one quasi-RCT,[17] and six observational studies[14,18–22]) comparing the perioperative discontinuation of immunosuppressive medication versus continuation. The timepoint and time interval of discontinuation of the immunosuppressive agent were very heterogeneous across studies, or not specified. Six (one RCT,[16] one quasi-RCT,[17] and four observational studies[18–20,22]) investigated methotrexate, and meta-analyses showed that the perioperative discontinuation of methotrexate might either be harmful or have no effect on SSI versus the continuation of methotrexate. The combined odds ratio (OR) was 7·75 (95% CI 1·66–36·24) for the controlled trials and 0·37 (0·07–1·89) for the observational studies. Two observational studies[14,21] investigated the use of anti-tumour necrosis factor (TNF). Meta-analysis showed that the perioperative

discontinuation of anti-TNF might have a benefit of reducing SSI compared with its continuation (OR 0·59; 0·37–0·95). The overall quality of the evidence was rated as very low. Considering the scarce (or absent) evidence to support discontinuation of treatment (anti-TNF) and even potential harm it may cause (methotrexate) such as the risk of flare-up of the underlying disease(s) associated with the suspension of therapy, immunosuppressive medication should not be discontinued to prevent SSI. The decision to discontinue the immunosuppressive medication should be made on an individual basis and involve the prescribing physician, the patient, and the surgeon.

Recommendation 2: enhanced nutritional support

The panel suggests considering the administration of oral or enteral multiple nutrient-enhanced nutritional formulas to prevent SSI in underweight patients who undergo major surgical operations (conditional recommendation, very low quality of evidence).

The nutritional status of patients can lead to alterations in host immunity that can make them more susceptible to postoperative infections. Early nutritional support can improve the outcome of major surgery and decrease the incidence of infectious complications in selected malnourished or severely injured patients.[23,24] Many researchers believe that nutritional interventions can reduce SSIs and associated morbidity. However, results related to the epidemiological association between incisional SSIs and malnutrition have varied, depending on the surgical subspecialties. We did a systematic review to investigate the effect of enhanced nutritional support versus standard nutrition for the prevention of SSI.

We identified ten studies (eight RCTs[25–32] and two observational studies[33,34]) comparing the use of multiple nutrient-enhanced nutritional formulas (containing any combination of arginine, glutamine, omega-3 fatty acids, and nucleotides) administered through oral and enteral routes with standard nutrition. Meta-analyses showed that a multiple nutrient-enhanced nutritional formula was associated with significantly reduced SSI incidence compared with a standard formula, both in the RCTs (combined OR 0·53; 95% CI 0·30–0·91) and the observational studies (combined OR 0·07; 0·01–0·53). The quality of the evidence was rated as very low. Six studies (five RCTs[32,35–38] and one observational study[39]) compared the use of nutritional supplements enhanced with a single nutrient (either arginine, glycine, or branched chain aminoacids) with standard nutrition. Meta-analyses showed no difference in the risk of SSI between the single nutrient-enhanced formula and standard nutrition in the RCTs (combined OR 0·61; 0·13–2·79) or the observational study (0·29; 0·06–1·39). The quality of evidence was rated as low.

In conclusion, multiple nutrient-enhanced formulas can be used to prevent SSIs in adult patients undergoing major surgery. However, the use of enhanced nutrition support is expensive and requires additional work for clinical staff, including expertise from dietitians and pharmacists. Notably, the availability of these nutrient products is low in LMICs. When considering this intervention in the context of a priority assessment approach to reduce the SSI risk, resources and product availability should be carefully assessed, particularly in settings with limited resources.

Recommendation 3: preoperative bathing

Good clinical practice requires that patients bathe or shower before surgery. The panel suggests that either a plain or antimicrobial soap can be used for this purpose (conditional recommendation, moderate quality of evidence).

Preoperative whole-body bathing or showering is considered to be good clinical practice to ensure that the skin is as clean as possible before surgery and reduce the bacterial load, particularly at the site of incision. In general, an antiseptic soap is used in settings in which it is available and affordable. We did a systematic review to assess whether using an antiseptic soap for preoperative bathing is more effective in reducing SSIs than using plain soap.

Nine studies (seven RCTs and two observational studies)[40–48] examined preoperative bathing or showering with an antiseptic soap compared with plain soap. A meta-analysis showed that bathing with a soap containing the antiseptic agent chlorhexidine gluconate did not significantly reduce SSI incidence compared with bathing with plain soap (combined OR 0·92; 95% CI 0·80–1·04). The quality of evidence was rated as moderate. We also assessed whether preoperative bathing with chlorhexidine gluconate-impregnated cloths is more effective than using an antiseptic soap. Very low quality evidence from three observational studies[49–51] showed that chlorhexidine gluconate cloths were associated with a decrease in SSI compared with no bathing (OR 0·27; 0·09–0·79). In conclusion, either a plain or antiseptic soap can be used for patient preoperative bathing, but the evidence was insufficient to formulate any recommendation on the use of chlorhexidine gluconate-impregnated cloths for the purpose of reducing SSIs.

Recommendations 4 and 5: decolonisation with mupirocin ointment with or without chlorhexidine gluconate body wash in nasal carriers undergoing surgery

The panel recommends that patients undergoing cardiothoracic and orthopaedic surgery who are known nasal carriers of Staphylococcus aureus, *should receive perioperative intranasal applications of mupirocin 2% ointment with or without a combination of chlorhexidine gluconate body wash (strong recommendation, moderate quality of evidence). The panel suggests considering the use of the same treatment in patients with known nasal carriage of* S aureus *undergoing other types of surgery (conditional recommendation, moderate quality of evidence).*

S aureus is one of, if not the most common health-care-associated pathogen worldwide, and can have severe consequences, including postoperative wound infection, nosocomial pneumonia, catheter-related bacteraemia, and increased mortality when it has meticillin resistance patterns.[52–54] *S aureus* nasal carriage is a well defined risk factor for subsequent infection in various patient groups. Mupirocin nasal ointment (usually applied twice daily for 5 days) is an effective, safe, and fairly cheap treatment for the eradication of *S aureus* carriage and is generally used in combination with a whole body wash. We did a systematic literature review to establish whether decolonisation with intranasal mupirocin ointment with or without a combination of chlorhexidine gluconate soap body wash reduces prevalence of *S aureus* overall infection, including SSIs.

Six RCTs comparing mupirocin nasal ointment with or without chlorhexidine gluconate soap body wash with placebo or no treatment were identified.[55–60] Overall, a meta-analysis showed that the use of mupirocin 2% ointment with or without a combination of chlorhexidine gluconate soap body wash has a marked benefit in reducing the SSI incidence due to *S aureus* in patients with nasal carriage compared with placebo or no treatment (OR 0·46; 95% CI 0·31–0·69), as well as the overall incidence of health-care-associated *S aureus* infection (0·48; 0·32–0·71). The quality of evidence was rated as moderate. Most studies included patients undergoing cardiothoracic and orthopaedic surgery, but two trials included other types of procedures. Furthermore, a meta-regression analysis showed that the effect on the *S aureus* infection prevalence did not differ between different types of surgery (p=0·986).

Considering that the evidence is most solid for cardiothoracic and orthopaedic patients, and considering the feasibility and cost issues in applying this intervention to all surgical patients, the panel suggest that perioperative intranasal applications of mupirocin 2% ointment with or without a combination of chlorhexidine gluconate body wash should be done in the patient population with known *S aureus* nasal carriage undergoing cardiothoracic or orthopaedic surgery. This intervention could also be considered in carriers undergoing other types of surgery while taking other factors into account, such as the local prevalence of SSIs caused by *S aureus* and meticillin-resistant *S aureus* and patient-related factors (eg, past *S aureus* infection, known carrier status of community-acquired meticillin-resistant *S aureus*, and *S aureus* colonisation in sites other than the nose). To avoid unnecessary treatment and resistance spread, this intervention should be done only on known *S aureus* carriers. Therefore, these recommendations apply to facilities where screening for *S aureus* is feasible, and indeed, studies were done mostly in high-income countries. Notably, the studies identified as the evidence base for these recommendations did not specifically assess screening for *S aureus* as part of the intervention. Consequently, no recommendation can be formulated on the role of screening for *S aureus* carriage in this context or the surgical patient population that should undergo screening.

Recommendations 6 and 7: mechanical bowel preparation and the use of oral antibiotics

The panel suggests that preoperative oral antibiotics combined with mechanical bowel preparation (MBP) should be used to reduce the risk of SSI in adult patients undergoing elective colorectal surgery (conditional recommendation, moderate quality evidence), and recommends that MBP alone (without administration of oral antibiotics) should not be used (strong recommendation, moderate quality evidence).

MBP involves the preoperative administration of substances (polyethylene glycol and sodium phosphate are the most widely used) to induce voiding of the intestinal and colonic contents. It is commonly believed to reduce the risk of postoperative infectious complications by decreasing the intraluminal faecal mass, thus theoretically decreasing the bacterial load in the intestinal lumen. The administration of oral antibiotics has been combined with MBP to further decrease the intraluminal bacterial load. We did a systematic review to investigate whether preoperative MBP is effective in reducing SSI incidence in colorectal surgery. The review assessed also whether combining the preoperative administration of oral antibiotics with MBP (in addition to the standard preoperative intravenous antibiotic prophylaxis) is more effective than MBP alone.

We identified 24 RCTs[61–84] that compared either MBP with no MBP or the combined intervention of MBP and oral antibiotics with MBP alone in adult patients undergoing colorectal surgical procedures. A meta-analysis of 11 RCTs[66,68,69,71,72,74,77,78,80–82] showed that preoperative MBP combined with oral antibiotics reduced SSI compared with MBP alone (combined OR 0·56; 95% CI 0·37–0·83). Meta-analysis of 13 RCTs[61–65,67,70,73,75,76,79,83,84] showed that preoperative MBP alone did not significantly affect incidence of SSIs compared with no MBP (combined OR 1·31; 95% CI: 0·99–1·72). Indeed, it was associated with a higher SSI risk, which approached statistical significance. The quality of evidence was rated as moderate for both comparisons. However, the protocols differed across trials in terms of dosage, timing of the application, fasting, and the agents used for MBP. The antibiotic regimens also differed, although aminoglycosides combined with anaerobic coverage (metronidazole or erythromycin) were the most frequently used.

Possible harms associated with MBP should be considered, such as patient discomfort, electrolyte abnormalities, potentially severe dehydration at the time of anaesthesia and incision, and acute phosphate nephropathy, associated with oral sodium phosphate.

Adverse effects of the oral antibiotics (eg, high risk of idiosyncratic reaction with erythromycin) and antimicrobial resistance can also occur.

In conclusion, preoperative oral antibiotics should be used in combination with MBP in adult patients undergoing elective colorectal surgery to reduce the risk of SSI. MBP should not be done alone without oral antibiotics. On the basis of the available evidence, no recommendation can be made on the preferred type of oral antibiotic, including the timing of administration and dosage, but an activity against both facultative Gram-negative and anaerobic bacteria should be guaranteed, and non-absorbable antibiotics should be used preferably. Ideally, the choice of antimicrobials should be made according to local availability, updated resistance data within institutions, and the volume of surgical activity. This intervention is for preoperative use only and should not be continued postoperatively. The use of oral antibiotics in association with MBP does not replace the need for intravenous surgical antibiotic prophylaxis.

Recommendation 8: hair removal

The panel recommends that in patients undergoing any surgical procedure, hair should either not be removed or, if absolutely necessary, it should be removed only with a clipper. Shaving is strongly discouraged at all times, whether preoperatively or in the operating room (strong recommendation, moderate quality of evidence).

Removal of hair from the intended site of surgical incision has traditionally been part of the routine preoperative preparation of patients. Hair is perceived to be associated with poor cleanliness and SSIs. Although hair removal might be necessary to facilitate adequate exposure and preoperative skin marking, the method used can cause microscopic trauma of the skin and increase the risk of SSIs. We did a systematic review to investigate whether the method (eg, using clippers, depilatory cream, or shaving with razors) and timing of hair removal versus no hair removal affect the incidence of SSIs. 15 RCTs or quasi-RCTs[85–99] comparing the effects of preoperative hair removal versus no hair removal or different methods of hair removal (shaving, clipping, and depilatory cream) were identified and several meta-analyses were done.

The three hair removal methods did not affect the incidence of SSIs compared with no hair removal. The combined ORs were 1·78 (95% CI 0·96–3·29) for shaving, 1·00 (0·06–16·34) for clipping, and 1·02 (0·42–2·49) for depilatory cream. The quality of evidence was rated as moderate. However, when hair is removed, clipping significantly reduces SSIs compared with shaving (OR 0·51; 0·29–0·91). Because they have similar potential to cause microscopic skin trauma, no hair removal and clipping were combined in an additional meta-analysis, which showed that they are associated with significantly reduced prevalence of SSIs compared with shaving (combined OR 0·51; 0·34–0·78). No recommendation regarding the timing of hair removal could be formulated as only one study assessed this question with no relevant results, but the panel suggested that removal by clipping shortly before surgery is the safest approach, if required.

Recommendations 9 and 10: optimal timing for administration of surgical antibiotic prophylaxis (SAP)

The panel recommends the administration of SAP before surgical incision when indicated, depending on the type of operation (strong recommendation, low quality of evidence); it should be done within the 120 min before the incision, while considering the half-life of the antibiotic (strong recommendation, moderate quality of evidence).

SAP refers to the prevention of infectious complications by administering an antimicrobial agent before exposure to contamination during surgery.[100] Successful SAP requires delivery of the antimicrobial agent in effective concentrations to the operative site through intravenous administration at the appropriate time. We did a systematic review to compare the effect of different timings of SAP administration on SSIs and to identify the optimal timing to prevent SSIs.

We identified 13 observational studies,[101–113] but no RCTs or studies in the paediatric population. We did several meta-analyses to assess different SAP timings. Low-quality evidence showed that the administration of SAP after incision was associated with a significantly higher incidence of SSI compared with administration before incision (combined OR 1·89; 95% CI 1·05–3·4). Moderate quality evidence showed that administration earlier than 120 min before incision was associated with a significantly higher prevalence of SSI compared with administration within 120 min (combined OR 5·26; 3·29–8·39). Further comparisons of administration within 60 min before incision compared with 60–120 min, or within 30 min before incision compared with 30–60 min, showed no significant difference in the reduction of SSIs. However, the quality of the evidence was rated as low.

On the basis of the available evidence, a more precise timing of less than 120 min before incision cannot be defined, and the widely implemented recommendation of within 60 min before incision is not supported by evidence. The half-life of the agent used, the underlying condition(s) of the individual patient (eg, body-mass index, or renal or liver function), the time needed to complete the procedure, and the protein binding of the antibiotic should be taken into account to achieve adequate serum and tissue concentrations at the surgical site at the time of incision and up to wound closure—in particular to prevent incisional SSI. For instance, administration should be closer to the incision time (<60 min before) for antibiotics with a short half-life, such as cefazolin and cefoxitin, and penicillins in general. Most available guidelines recommend a single preoperative dose; intraoperative

redosing is indicated if the duration of the procedure exceeds two half-lives of the drug, or if there is excessive blood loss during the procedure. However, these concepts are not based on clinical outcome data. A specific WHO recommendation on the duration of SAP is detailed in paper 2 of this Series.[13]

Recommendation 11: surgical hand preparation

The panel recommends that surgical hand preparation be done either by scrubbing with a suitable antimicrobial soap and water or using a suitable alcohol-based hand rub (ABHR) before donning sterile gloves (strong recommendation, moderate quality of evidence).

Surgical hand preparation (figure) is vitally important to maintain the least possible contamination of the surgical field, especially in the case of sterile glove puncture during the procedure. Appropriate surgical hand preparation is recommended in the WHO guidelines on hand hygiene in health care issued in 2009[114] and in all other existing national and international guidelines for the prevention of SSIs. We did a systematic review to compare the effect of different techniques (ie, hand rubbing *vs* hand scrubbing), products (ie, different formulations of ABHRs *vs* plain soap *vs* medicated soap), and application times for the same product.

We only found six studies (three RCTs[115–117] and three observational studies[118–120]) with SSI as the primary outcome that compared hand rubbing with hand scrubbing using different products. Five studies compared ABHR with hand scrubbing with an antimicrobial soap containing either 4% povidone-iodine or 4% chlorhexidine gluconate and showed no significant difference in SSI incidence.[115,117–120] Additionally, no significant difference was seen in a cluster randomised cross-over trial comparing ABHR to hand scrubbing with plain soap.[116] It was not possible to do any meta-analysis of these data because the products used for hand rubbing or scrubbing were different. The overall evidence (rated as moderate quality) showed no difference between hand rubbing and hand scrubbing in reducing SSI incidence. Evidence from additional studies using the bacterial load on participants' hands as the outcome showed that some ABHR formulations are more effective to reduce colony-forming units than scrubbing with water and antiseptic or plain soap. However, the relevance of this outcome to the risk of SSI is uncertain. Because of the use of different protocols, it was not possible to identify optimal application times for the two techniques. When selecting an ABHR, health-care facilities should procure products with proven efficacy according to international standards and position no-touch or elbow-operated dispensers in surgical scrub rooms. In LMICs in which ABHR availability might be low, WHO strongly encourages facilities to undertake the local production of an alcohol-based formulation, which has been shown to be a feasible and low-cost solution.[121,122] Alternatively, antimicrobial soap, clean running water, and disposable or clean towels for each health-care worker should be available in the scrub room.

Figure: **Surgical staff performing surgical hand rubbing before entering the operating room**
Courtesy of Didier Pittet.

Recommendation 12: surgical site skin preparation

The panel recommends alcohol-based antiseptic solutions that are based on chlorhexidine gluconate for surgical site skin preparation in patients undergoing surgical procedures (strong recommendation, low to moderate quality of evidence).

The aim of surgical site skin preparation is to reduce the microbial load on the patient's skin as much as possible before incision of the skin barrier. The most common agents include chlorhexidine gluconate and povidone-iodine in alcohol-based solutions, but aqueous solutions are also widely used in LMICs, particularly those containing iodophors. We did a systematic review to compare the effect of different solutions used for the prevention of SSI—ie, alcohol-based versus aqueous preparations and antiseptic agents.

We identified 17 RCTs[123–139] comparing antiseptic agents (povidone-iodine and chlorhexidine gluconate) in aqueous or alcohol-based solutions. Overall, a meta-analysis of 12 RCTs[124,126–133,135–137] showed that alcohol-based antiseptic solutions were more effective than aqueous solutions in reducing the risk of SSI (combined OR 0·60; 95% CI 0·45–0·78). More specifically, a significant reduction of the SSI risk was shown with the use of alcohol-based chlorhexidine gluconate compared with either aqueous povidone-iodine (combined OR 0·65; 0·47–0·90) or povidone-iodine in alcohol-based solutions (0·58; 0·42–0·80). The quality of evidence was rated as low to moderate.

Operating room staff should be trained and informed about the potential harms associated with the solutions used for surgical site preparation. Alcohol-based solutions should not be used on neonates or come into

Search strategy and selection criteria

For each population, intervention, comparator, outcomes question, we searched MEDLINE (PubMed or Ovid), Embase, Cumulative Index to Nursing and Allied Health Literature, the Cochrane Central Register of Controlled Trials, and WHO regional medical databases, to identify relevant articles. The time limit was January, 1990, and the systematic reviews were done between December, 2013, and December, 2015. Studies in English, French, and Spanish were eligible; but some reviews were not restricted by language. A comprehensive list of search terms was used, including medical subject headings.

contact with mucosa or eyes, and caution should be exercised because of their flammable nature. Chlorhexidine gluconate solutions can cause skin irritation and must not be allowed to come into contact with the brain, meninges, eye, or middle ear. Notably, alcohol-based solutions might be difficult to procure and expensive in LMICs, particularly when combined with an antiseptic compound. Local production could be a more affordable and feasible option in these settings, provided that adequate quality control is in place.

Recommendation 13: antimicrobial skin sealants

The panel suggests that antimicrobial sealants should not be used after surgical site skin preparation for the purpose of reducing SSI (conditional recommendation, very low quality of evidence).

Antimicrobial skin sealants are sterile, film-forming cyanoacrylate-based sealants commonly applied as an additional antiseptic measure after using standard skin preparation on the surgical site and before skin incision. They are intended to remain in place and block the migration of flora from the surrounding skin into the surgical site by dissolving over several days post-operatively. We did a systematic review to investigate whether the use of antimicrobial skin sealants in addition to standard surgical site skin preparation is more effective in reducing the risk of SSI than standard surgical site skin preparation only.

Nine studies (eight RCTs[140–147] and one prospective, quasi-RCT[148]) were identified. Meta-analysis showed no benefit or harm for the reduction of SSI with the addition of antimicrobial sealants compared with standard surgical site skin preparation only (OR 0·69; 95% CI 0·38–1·25). Therefore—also to avoid unnecessary costs—antimicrobial sealants should not be used after surgical site skin preparation for the purpose of reducing SSIs.

Conclusion

We have discussed the evidence for a broad range of preventive measures identified by an expert panel that potentially contribute to reducing the risk of SSI occurrence. For some of these, the evidence shows no benefit and the expert panel advises against the adoption of these interventions, particularly when considering resource implications or other consequences, such as antimicrobial resistance. However, the panel identified a range of key measures for SSI prevention to be implemented in the preoperative period, together with the intraoperative and postoperative periods discussed in paper 2 of this Series. Adoption should be facilitated by sound implementation strategies and practical tools. Notably, careful assessment of feasibility and cost implications in low-resource settings is needed.

For the **full WHO Guidelines for the Prevention of Surgical Site Infection** see http://www.who.int/gpsc/ssi-guidelines/en/index.html

Contributors

BA led the writing of and PB, SdJ, NZK, BZ, DP, MA, and JSS contributed to the manuscript. All authors contributed to the development of the WHO Global Guidelines for the Prevention of Surgical Site Infection. BA, PB, SdJ, NZK, BZ, SMG, JJA, SGa, MvR, MAB, ME, JK, and JSS contributed to the performance and interpretation of systematic reviews and meta-analyses.

Declaration of interests

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