

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

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44 **1 Table and 1 Figure**

45 **Table 1:** Summary of measures implemented or initiated during the preoperative period and related
46 WHO recommendations for the prevention of SSIs*

47 **Figure 1:** Surgical staff performing surgical hand rubbing before entering the operating room

48 Courtesy of Didier Pittet.

49 **ABSTRACT**

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

61

62 **INTRODUCTION**

63 Health-care-associated infections are avoidable infections that affect hundreds of millions of people
64 each year worldwide. Following a systematic review of the literature and meta-analyses, WHO
65 reported in 2010 that the prevalence of health-care-associated infections in low-income and middle-
66 income countries (LMICs) was two to 20 times higher than in high-income countries.¹⁻³ Surgical site
67 infection (SSI) was the most surveyed and most frequent health-care-associated infection in LMICs,
68 affecting up to a third of patients who had surgery. The incidence of SSI is much lower in high-
69 income countries, but it is still the second most common cause of health-care-associated infection in
70 Europe and the USA.^{1,4} Furthermore, data from the USA showed that up to 60% of the
71 microorganisms isolated from infected surgical wounds have antibiotic resistance patterns.⁵
72 Considering the epidemiological importance of SSIs, and the fact that these infections are largely
73 preventable, WHO decided to prioritise the development of evidence-based recommendations for
74 the prevention of SSIs. Many factors in the patient's journey through surgery contribute to the risk

75 of SSI, and prevention is complex and requires the integration of a range of measures before, during,
76 and after surgery. Further strong reasons to develop global guidelines on this topic include the
77 absence of any international guidance document and inconsistencies in the interpretation of the
78 evidence and strength of recommendations in national guidelines. We present the WHO
79 recommendations for measures to be implemented or initiated during the preoperative period.
80 These were elaborated according to the best available scientific evidence and expert consensus with
81 the aim to ensure high-quality care for every patient, irrespective of the resources available.
82 Important topics such as SSI surveillance are not mentioned in this Review because formal
83 recommendations have not been made, but they are extensively reviewed in the WHO guidelines as
84 cornerstones of SSI prevention. The intended audience for these recommendations is primarily the
85 surgical team (ie, surgeons, nurses, technical support staff, anaesthetists, and any professionals
86 directly providing surgical care), infection prevention and control professionals, policymakers, senior
87 managers, and hospital administrators. People responsible for staff education and training are also
88 key stakeholders and implementers.

89

90 **METHODS**

91 **Data gathering**

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

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

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

105

106 **Data analysis and the development of recommendations**

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

124

125 **RECOMMENDATION 1: PERIOPERATIVE DISCONTINUATION OF IMMUNOSUPPRESSIVE AGENTS**

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

128 used for preventing the rejection of transplanted organs or for the treatment of inflammatory
129 diseases could lead to impaired wound healing and an increased risk of infection in patients
130 administered these agents.¹⁴ By contrast, the discontinuation of immunosuppressive treatment
131 could induce flares of disease activity, and long-term interruptions of therapy might induce the
132 formation of anti-drug antibodies and subsequently decrease their effect.¹⁵ We did a systematic
133 review and meta-analyses to assess whether the discontinuation of immunosuppressive therapy in
134 the perioperative period is effective to prevent SSIs in patients who undergo surgery.

135 We identified eight studies (one RCT,¹⁶ one quasi-RCT,¹⁷ and six observational studies^{14,18–22}) com
136 paring the perioperative discontinuation of immune-suppressive medication versus continuation.

137 The timepoint and time interval of discontinuation of the immunosuppressive agent were very
138 heterogeneous across studies, or not specified. Six (one RCT,¹⁶ one quasi-RCT,¹⁷ and four
139 observational studies^{18–20,22}) investigated methotrexate, and meta-analyses showed that the
140 perioperative discontinuation of methotrexate might either be harmful or have no effect on SSI
141 versus the continuation of methotrexate. The combined odds ratio (OR) was 7.75 (95% CI 1.66–
142 36.24) for the controlled trials and 0.37 (0.07–1.89) for the observational studies. Two observational
143 studies^{14,21} investigated the use of anti-tumour necrosis factor (TNF). Meta-analysis showed that the
144 perioperative discontinuation of anti-TNF might have a benefit of reducing SSI compared with its
145 continuation (OR 0.59; 0.37–0.95). The overall quality of the evidence was rated as very low.

146 Considering the scarce (or absent) evidence to support discontinuation of treatment (anti-TNF) and
147 even potential harm it may cause (methotrexate) such as the risk of flare-up of the underlying
148 disease(s) associated with the suspension of therapy, immunosuppressive medication should not be
149 discontinued to prevent SSI. The decision to discontinue the immunosuppressive medication should
150 be made on an individual basis and involve the prescribing physician, the patient, and the surgeon.

151 **RECOMMENDATION 2: ENHANCED NUTRITIONAL SUPPORT**

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

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

163 We identified ten studies (eight RCTs²⁵⁻³² and two observational studies^{33,34}) comparing the use of
164 multiple nutrient-enhanced nutritional formulas (containing any combination of arginine, glutamine,
165 omega-3 fatty acids, and nucleotides) administered through oral and enteral routes with standard
166 nutrition. Meta-analyses showed that a multiple nutrient-enhanced nutritional formula was
167 associated with significantly reduced SSI incidence compared with a standard formula, both in the
168 RCTs (combined OR 0.53; 95% CI 0.30-0.91) and the observational studies (combined OR 0.07; 0.01-
169 0.53). The quality of the evidence was rated as very low. Six studies (five RCTs^{32,35-38} and one
170 observational study³⁹) compared the use of nutritional supplements enhanced with a single nutrient
171 (either arginine, glycine, or branched chain aminoacids) with standard nutrition. Meta-analyses
172 showed no difference in the risk of SSI between the single nutrient-enhanced formula and standard
173 nutrition in the RCTs (combined OR 0.61; 0.13-2.79) or the observational study (0.29; 0.06-1.39). The
174 quality of evidence was rated as low.

175 In conclusion, multiple nutrient-enhanced formulas can be used to prevent SSIs in adult patients
176 undergoing major surgery. However, the use of enhanced nutrition support is expensive and requires

177 additional work for clinical staff , including expertise from dietitians and pharmacists. Notably, the
178 availability of these nutrient products is low in LMICs. When considering this intervention in the
179 context of a priority assessment approach to reduce the SSI risk, resources and product availability
180 should be carefully assessed, particularly in settings with limited resources.

181

182 **RECOMMENDATION 3: PREOPERATIVE BATHING**

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

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

191 Nine studies (seven RCTs and two observational studies)⁴⁰⁻⁴⁸ examined preoperative bathing or
192 showering with an antiseptic soap compared with plain soap. A meta-analysis showed that bathing
193 with a soap containing the antiseptic agent chlorhexidine gluconate did not significantly reduce SSI
194 incidence compared with bathing with plain soap (combined OR 0.92; 95% CI 0.80-1.04). The quality
195 of evidence was rated as moderate. We also assessed whether preoperative bathing with
196 chlorhexidine gluconate-impregnated cloths is more effective than using an antiseptic soap. Very low
197 quality evidence from three observational studies⁴⁹⁻⁵¹ showed that chlorhexidine gluconate cloths
198 were associated with a decrease in SSI compared with no bathing (OR 0.27; 0.09-0.79). In conclusion,
199 either a plain or antiseptic soap can be used for patient preoperative bathing, but the evidence was
200 insufficient to formulate any recommendation on the use of chlorhexidine gluconate-impregnated
201 cloths for the purpose of reducing SSIs.

202

203 **RECOMMENDATION 4 AND 5: DECOLONISATION WITH MUPIROCIN OINTMENT WITH OR WITHOUT**
204 **CHLORHEXIDINE GLUCONATE BODY WASH IN NASAL CARRIERS UNDERGOING SURGERY**

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

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

220 Six RCTs comparing mupirocin nasal ointment with or without chlorhexidine gluconate soap body
221 wash with placebo or no treatment were identified.^{55–60} Overall, a meta-analysis showed that the use
222 of mupirocin 2% ointment with or without a combination of chlorhexidine gluconate soap body wash
223 has a marked benefit in reducing the SSI incidence due to *S aureus* in patients with nasal carriage
224 compared with placebo or no treatment (OR 0.46; 95% CI 0.31–0.69), as well as the overall incidence
225 of health-care-associated *S aureus* infection (0.48; 0.32–0.71). The quality of evidence was rated as
226 moderate. Most studies included patients undergoing cardiothoracic and orthopaedic surgery, but
227 two trials included other types of procedures. Furthermore, a meta-regression analysis showed that

228 the effect on the *S aureus* infection prevalence did not differ between different types of surgery
229 ($p=0.986$).

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

246

247 **RECOMMENDATION 6 AND 7: MECHANICAL BOWEL PREPARATION AND THE USE OF ORAL**
248 **ANTIBIOTICS**

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

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

263 We identified 24 RCTs⁶¹⁻⁸⁴ that compared either MBP with no MBP or the combined intervention of
264 MBP and oral antibiotics with MBP alone in adult patients undergoing colorectal surgical procedures.

265 A meta-analysis of 11 RCTs^{66,68,69,71,72,74,77,78,80-82} showed that preoperative MBP combined with oral
266 antibiotics reduced SSI compared with MBP alone (combined OR 0.56; 95% CI 0.37-0.83). Meta-
267 analysis of 13 RCTs^{61-65,67,70,73,75,76,79,83,84} showed that preoperative MBP alone did not significantly
268 affect incidence of SSIs compared with no MBP (combined OR 1.31; 95% CI: 0.99-1.72). Indeed, it was
269 associated with a higher SSI risk, which approached statistical significance. The quality of evidence was
270 rated as moderate for both comparisons. However, the protocols differed across trials in terms of
271 dosage, timing of the application, fasting, and the agents used for MBP. The antibiotic regimens also
272 differed, although amino glycosides combined with anaerobic coverage (metro nidazole or
273 erythromycin) were the most frequently used.

274 Possible harms associated with MBP should be considered, such as patient discomfort, electrolyte
275 abnormalities, potentially severe dehydration at the time of anaesthesia and incision, and acute
276 phosphate nephropathy, associated with oral sodium phosphate. Adverse effects of the oral
277 antibiotics (eg, high risk of idiosyncratic reaction with erythromycin) and antimicrobial resistance can
278 also occur.

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

289

290 **RECOMMENDATION 8: HAIR REMOVAL**

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

295 Removal of hair from the intended site of surgical incision has traditionally been part of the routine
296 preoperative preparation of patients. Hair is perceived to be associated with poor cleanliness and SSIs.
297 Although hair removal might be necessary to facilitate adequate exposure and preoperative skin
298 marking, the method used can cause microscopic trauma of the skin and increase the risk of SSIs. We
299 did a systematic review to investigate whether the method (eg, using clippers, depilatory cream, or
300 shaving with razors) and timing of hair removal versus no hair removal affect the incidence of SSIs. 15
301 RCTs or quasi-RCTs⁸⁵⁻⁹⁹ comparing the effects of preoperative hair removal versus no hair removal or
302 different methods of hair removal (shaving, clipping, and depilatory cream) were identified and
303 several meta-analyses were done.

304 The three hair removal methods did not affect the incidence of SSIs compared with no hair removal.
305 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
306 (0.42–2.49) for depilatory cream. The quality of evidence was rated as moderate. However, when hair
307 is removed, clipping significantly reduces SSIs compared with shaving (OR 0.51; 0.29–0.91). Because
308 they have similar potential to cause microscopic skin trauma, no hair removal and clipping were
309 combined in an additional meta-analysis, which showed that they are associated with significantly
310 reduced prevalence of SSIs compared with shaving (combined OR 0.51; 0.34–0.78). No
311 recommendation regarding the timing of hair removal could be formulated as only one study assessed
312 this question with no relevant results, but the panel suggested that removal by clipping shortly before
313 surgery is the safest approach, if required.

314

315 **RECOMMENDATION 9 AND 10: OPTIMAL TIMING FOR ADMINISTRATION OF SURGICAL ANTIBIOTIC**
316 **PROPHYLAXIS (SAP)**

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

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

326 We identified 13 observational studies,^{101–113} but no RCTs or studies in the paediatric population. We
327 did several meta-analyses to assess different SAP timings. Low-quality evidence showed that the
328 administration of SAP after incision was associated with a significantly higher incidence of SSI
329 compared with administration before incision (combined OR 1.89; 95% CI 1.05–3.4). Moderate quality

330 evidence showed that administration earlier than 120 min before incision was associated with a
331 significantly higher prevalence of SSI compared with administration within 120 min (combined OR
332 5.26; 3.29–8.39). Further comparisons of administration within 60 min before incision compared with
333 60–120 min, or within 30 min before incision compared with 30–60 min, showed no significant
334 difference in the reduction of SSIs. However, the quality of the evidence was rated as low.

335 On the basis of the available evidence, a more precise timing of less than 120 min before incision
336 cannot be defined, and the widely implemented recommendation of within 60 min before incision is
337 not supported by evidence. The half-life of the agent used, the underlying condition(s) of the individual
338 patient (eg, bodymass index, or renal or liver function), the time needed to complete the procedure,
339 and the protein binding of the antibiotic should be taken into account to achieve adequate serum and
340 tissue concentrations at the surgical site at the time of incision and up to wound closure—in particular
341 to prevent incisional SSI. For instance, administration should be closer to the incision time (<60 min
342 before) for antibiotics with a short half-life, such as cefazolin and ceftiofur, and penicillins in general.
343 Most available guidelines recommend a single preoperative dose; intraoperative redosing is indicated
344 if the duration of the procedure exceeds two half-lives of the drug, or if there is excessive blood loss
345 during the procedure. However, these concepts are not based on clinical outcome data. A specific
346 WHO recommendation on the duration of SAP is detailed in paper 2 of this Series.¹³

347

348 **RECOMMENDATION 11: SURGICAL HAND PREPARATION**

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

352 Surgical hand preparation (figure) is vitally important to maintain the least possible contamination of
353 the surgical field, especially in the case of sterile glove puncture during the procedure. Appropriate
354 surgical hand preparation is recommended in the WHO guidelines on hand hygiene in health care
355 issued in 2009¹¹⁴ and in all other existing national and international guidelines for the prevention of

356 SSIs. We did a systematic review to compare the effect of different techniques (ie, hand rubbing vs
357 hand scrubbing), products (ie, different formulations of ABHRs vs plain soap vs medicated soap), and
358 application times for the same product.

359 We only found six studies (three RCTs¹¹⁵⁻¹¹⁷ and three observational studies¹¹⁸⁻¹²⁰) with SSI as the
360 primary outcome that compared hand rubbing with hand scrubbing using different products. Five
361 studies compared ABHR with hand scrubbing with an antimicrobial soap containing either 4%
362 povidone-iodine or 4% chlorhexidine gluconate and showed no significant difference in SSI
363 incidence.^{115,117-120} Additionally, no significant difference was seen in a cluster randomised cross-over
364 trial comparing ABHR to hand scrubbing with plain soap.¹¹⁶ It was not possible to do any meta-analysis
365 of these data because the products used for hand rubbing or scrubbing were different. The overall
366 evidence (rated as moderate quality) showed no difference between hand rubbing and hand
367 scrubbing in reducing SSI incidence. Evidence from additional studies using the bacterial load on
368 participants' hands as the outcome showed that some ABHR formulations are more effective to
369 reduce colony-forming units than scrubbing with water and antiseptic or plain soap. However, the
370 relevance of this outcome to the risk of SSI is uncertain. Because of the use of different protocols, it
371 was not possible to identify optimal application times for the two techniques. When selecting an
372 ABHR, health-care facilities should procure products with proven efficacy according to international
373 standards and position no-touch or elbow-operated dispensers in surgical scrub rooms. In LMICs in
374 which ABHR availability might be low, WHO strongly encourages facilities to undertake the local
375 production of an alcohol-based formulation, which has been shown to be a feasible and low-cost
376 solution.^{121,122} Alternatively, antimicrobial soap, clean running water, and disposable or clean towels
377 for each health-care worker should be available in the scrub room.

378

379 **RECOMMENDATION 12: SURGICAL SITE SKIN PREPARATION**

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

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

389 We identified 17 RCTs^{123–139} comparing antiseptic agents (povidone-iodine and chlorhexidine
390 gluconate) in aqueous or alcohol-based solutions. Overall, a meta-analysis of 12 RCTs^{124,126–133,135–137}
391 showed that alcohol-based antiseptic solutions were more effective than aqueous solutions in
392 reducing the risk of SSI (combined OR 0.60; 95% CI 0.45–0.78). More specifically, a significant
393 reduction of the SSI risk was shown with the use of alcohol-based chlorhexidine gluconate compared
394 with either aqueous povidone-iodine (combined OR 0.65; 0.47–0.90) or povidone-iodine in alcohol-
395 based solutions (0.58; 0.42–0.80). The quality of evidence was rated as low to moderate.

396 Operating room staff should be trained and informed about the potential harms associated with the
397 solutions used for surgical site preparation. Alcohol-based solutions should not be used on neonates
398 or come into contact with mucosa or eyes, and caution should be exercised because of their
399 flammable nature. Chlorhexidine gluconate solutions can cause skin irritation and must not be allowed
400 to come into contact with the brain, meninges, eye, or middle ear. Notably, alcohol-based solutions
401 might be difficult to procure and expensive in LMICs, particularly when combined with an antiseptic
402 compound. Local production could be a more affordable and feasible option in these settings,
403 provided that adequate quality control is in place.

404

405 **RECOMMENDATION 13: ANTIMICROBIAL SKIN SEALANTS**

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

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

415 Nine studies (eight RCTs^{140–147} and one prospective, quasi-RCT¹⁴⁸) were identified. Meta-analysis
416 showed no benefit or harm for the reduction of SSI with the addition of antimicrobial sealants
417 compared with standard surgical site skin preparation only (OR 0·69; 95% CI 0·38–1·25). Therefore—
418 also to avoid unnecessary costs—antimicrobial sealants should not be used after surgical site skin
419 preparation for the purpose of reducing SSIs.

420

421 **CONCLUSION**

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

430 settings is needed.

431

432 **Box: Search strategy and selection criteria**

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

440

441 **Contributors**

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

446

447 **Declaration of interests**

448 MA received grants and non-financial support from the Innovative Medicines Initiative Joint
449 Undertaking under the Combatting Bacterial Resistance in Europe (COMBACTE-Net) grant
450 agreement (no 115523). These resources are composed of financial contributions from the European
451 Union's 7th Framework Programme (FP7/2007–2013) and the European Federation of
452 Pharmaceutical Industries and Associations companies' in-kind contribution during the study. MAB
453 has previously received a research grant from Johnson & Johnson, and also grants or honoraria for
454 delivering lectures on surgical site infection or serving on scientific advisory boards for

455 Abbott/Mylan, Acelity, Bard, Baxter, GlaxoSmithKline, Ipsen, and Johnson & Johnson. ME received
456 personal fees from the WHO during the study. All other authors declare no competing interests.

457 **Acknowledgments**

458 This article should be read in combination with the second paper in this Series on the new WHO
459 recommendations on intraoperative and postoperative measures to be implemented for the
460 prevention of SSI. These papers are an abbreviated version of the full WHO Guidelines for the
461 Prevention of Surgical Site Infection, which was published simultaneously on Nov 3, 2016. The
462 development of the guidelines was supervised by a WHO Steering Committee and we thank the
463 following members: Sergey Eremin, Edward Kelley, Walter Johnson, and valeska Stempliuk. We
464 thank the following experts who served on the Systematic Reviews Expert Group: Fleur de Vries,
465 Xiuwen Wu, Jianan Ren, Xavier Guirao, Sandra Pequeño, Petra Gastmeier, and Caroline Landelle. We
466 are grateful to the following experts who served as external peer reviewers of the draft guideline
467 documents: Emmanuel Ameh, Stephan Harbarth, Kamal Itani, Fernando Otaíza, Val Robertson, and
468 Ilker Uçkay. We also thank Rosemary Sudan for editing assistance, and Tomas Allen and Jose Luis
469 Garnica Carreno who provided assistance for the systematic review searches. Funding for the
470 development of these guidelines was mainly provided by WHO; also partly funded by the UK
471 Government's Fleming Fund; however, the views expressed do not necessarily reflect the official
472 policies of the UK Government; the Swiss Government and OASIS Global (Cincinnati, OH, USA) also
473 provided essential financial support. The systematic reviews done by the external expert teams were
474 done free of charge as in-kind contributions by the following institutions: Amphia Hospital Breda
475 (Breda, Netherlands); Academic Medical Center Amsterdam (Amsterdam, Netherlands), University
476 of Berlin (Berlin, Germany), University of Cincinnati (Cincinnati, OH, USA); Hospital Universitari Parc
477 Tauli, Sabadell (Barcelona, Spain); Jinling Hospital and the Medical School of Nanjing University
478 (Nanjing, China).

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- 865

866 **TABLE 1**

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

	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 <i>Staphylococcus aureus</i> undergoing cardiothoracic and orthopaedic surgery	Is mupirocin nasal ointment in combination with or without a CHG body wash effective in reducing the number of <i>S aureus</i> infections in nasal carriers undergoing cardiothoracic and orthopaedic surgery?	Patients with known nasal carriage of <i>S aureus</i> 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 body wash in nasal carriers of <i>S aureus</i> undergoing other types of surgery	Is mupirocin nasal ointment in combination with or without a CHG body wash effective in reducing the number of <i>S aureus</i> infections in nasal carriers undergoing other types of surgery?	Perioperative intranasal applications of mupirocin 2% ointment with or without a combination of CHG body wash 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)

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	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 2³ of this surgical site infections Series, to be read in combination with this Review. †The Grading of Recommendations Assessment, Development, and Evaluation method^{21,22} 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.

870 **FIGURE 1:** Surgical staff performing surgical hand rubbing before entering the operating room

871 Courtesy of Didier Pittet.



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