

Towards a consensus definition of maternal sepsis: results of a systematic review and expert consultation

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Reproductive Health

Towards a Consensus Definition of Maternal Sepsis: Results of a Systematic Review and Expert Consultation --Manuscript Draft--

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Abstract:	<p>Background: There is a need for a clear and actionable definition of maternal sepsis, in order to better assess the burden of this condition, trigger timely and effective treatment and allow comparisons across facilities and countries. The objective of this study was to review maternal sepsis definitions and identification criteria and to report on results of an expert consultation to develop a new international definition of maternal sepsis.</p> <p>Methods: All original and review articles and WHO documents, as well as clinical guidelines providing definitions and/or identification criteria of maternal sepsis were included. A multidisciplinary international panel of experts was surveyed through an online consultation in March-April 2016 on their opinion on the existing sepsis definitions, including new definition of sepsis proposed for the adult population (2016 Third International Consensus Definitions for Sepsis and Septic Shock) and importance of different criteria for identification of maternal sepsis. The definition was agreed in an expert face-to-face meeting convened by WHO and Jhpiego.</p> <p>Results: Standardizing the definition of maternal sepsis and aligning it with the current understanding of sepsis in the adult population was considered a mandatory step to improve the assessment of the burden of maternal sepsis by the expert panel. The literature review and expert consultation resulted in a new WHO consensus definition "Maternal sepsis is a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, child-birth, post-abortion, or post-partum period". Plans are in progress to validate the new WHO definition of maternal sepsis in a large international population.</p> <p>Conclusion: The operationalization of the new maternal sepsis definition requires generation of a set of practical criteria to identify women with sepsis. These criteria should enable clinicians to focus on the timely initiation of actionable elements of care (administration of antimicrobials and fluids, support of vital organ functions, referral) and improve maternal outcomes.</p>	
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1 **Title**

2 Towards a Consensus Definition of Maternal Sepsis: Results of a Systematic Review
3
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5 and Expert Consultation
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7 **4 Short title**

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10 Consensus Definition of Maternal Sepsis

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26 **Abstract**

27 **Background:** There is a need for a clear and actionable definition of maternal sepsis, in order
28 to better assess the burden of this condition, trigger timely and effective treatment and allow
29 comparisons across facilities and countries. The objective of this study was to review maternal
30 sepsis definitions and identification criteria and to report on results of an expert consultation
31 to develop a new international definition of maternal sepsis.

32 **Methods:** All original and review articles and WHO documents, as well as clinical guidelines
33 providing definitions and/or identification criteria of maternal sepsis were included. A
34 multidisciplinary international panel of experts was surveyed through an online consultation in
35 March-April 2016 on their opinion on the existing sepsis definitions, including new definition of
36 sepsis proposed for the adult population (2016 Third International Consensus Definitions for
37 Sepsis and Septic Shock) and importance of different criteria for identification of maternal
38 sepsis. The definition was agreed in an expert face-to-face meeting convened by WHO and
39 Jhpiego.

40 **Results:** Standardizing the definition of maternal sepsis and aligning it with the current
41 understanding of sepsis in the adult population was considered a mandatory step to improve
42 the assessment of the burden of maternal sepsis by the expert panel. The literature review and
43 expert consultation resulted in a new WHO consensus definition “Maternal sepsis is a life-
44 threatening condition defined as organ dysfunction resulting from infection during pregnancy,
45 child-birth, post-abortion, or post-partum period”. Plans are in progress to validate the new
46 WHO definition of maternal sepsis in a large international population.

47 **Conclusion:** The operationalization of the new maternal sepsis definition requires generation
48 of a set of practical criteria to identify women with sepsis. These criteria should enable
49 clinicians to focus on the timely initiation of actionable elements of care (administration of
50 antimicrobials and fluids, support of vital organ functions, referral) and improve maternal
51 outcomes.

52 **Key-words:** sepsis, maternal sepsis, consensus, definition

53 **Plain English summary**

54 Sepsis occurs when the body's response to infection damage its own organs and tissues. If not
55 recognised early and treated timely, sepsis can progress to shock and death. Physiological,
56 immunological and mechanical changes in pregnancy make pregnant women more susceptible
57 to infections compared with non-pregnant women. Furthermore, physiological adaptations to
58 pregnancy may obscure signs and symptoms of infection and sepsis.

59 Efforts have been made in the last 20 years to standardize definitions of sepsis for the general
60 adult population, but the validity and applicability of the proposed definition and identification
61 criteria to pregnant women are uncertain.

62 We reviewed articles and WHO documents, as well as clinical guidelines providing definitions
63 and/or identification criteria of maternal sepsis. We also surveyed a multidisciplinary
64 international panel of experts on their opinion on the existing sepsis definitions and
65 importance of different criteria for identification of maternal sepsis. The literature review and
66 expert consultation resulted in a new WHO consensus definition. These identification criteria
67 should enable clinicians to focus on the timely initiation of actionable elements of care
68 (administration of antimicrobials and fluids, support of vital organ functions, referral) and
69 improve maternal outcomes. Plans are in progress to validate the new WHO definition of
70 maternal sepsis in a large international population.

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79 Introduction

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2 80 Sepsis is a major public health concern[1]. Sepsis includes three essential components:
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4 81 infection, host response to infection and organ dysfunction. A wide range of pathogens could
5
6 82 cause life threatening responses in many organs; consequently sepsis has a broad spectrum of
7
8 83 clinical presentations. Pregnant women are particularly predisposed to develop infections and
9
10 84 sepsis for several reasons. Physiological, immunological and mechanical changes in pregnancy
11
12 85 make pregnant women more susceptible to infections compared with non-pregnant women,
13
14 86 particularly during the postpartum period[2]. Furthermore, physiological adaptations to
15
16 87 pregnancy (e.g. hyperdynamic circulation, tachycardia, diminished oxygen reserve,
17
18 88 hypercoagulability), blood loss, maternal efforts during second stage of labour, or
19
20 89 interventions during labour, may obscure signs and symptoms of infection and sepsis[3],[4].
21
22 90 This may result in delays in the recognition and treatment of sepsis[5]. Another factor to be
23
24 91 considered is that a substantial proportion of early onset neonatal sepsis originates from intra-
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26 92 uterine infections and antepartum maternal infections.
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35 94 Globally, important achievements in healthcare (for example, hand washing, antibiotics)[6]
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37 95 had a great impact on the reduction of infection-related maternal deaths; however sepsis is
38
39 96 still an important contributor to preventable maternal mortality. Infections are considered the
40
41 97 underlying cause in about 11% of maternal deaths[7] and are a significant contributor to many
42
43 98 deaths attributed to other conditions. However, the true frequency of maternal infections and
44
45 99 its complications are not well known. Imprecise and varying definitions may have led to
46
47 100 discrepancies in reported incidence and observed mortality[1, 2, 8]. Available data on
48
49 101 pregnancy associated sepsis from high-income countries report an incidence of 9 to 49 per
50
51 102 100,000 deliveries-years, depending on the definition and population used[9]. Lack of data
52
53 103 from low-income countries makes the incidence difficult to determine in those countries[10].
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55 104 Compared to other pregnancy complications the case fatality rate of maternal sepsis is very
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105 high. Sepsis with acute organ dysfunction has a mortality of 20–40% in high-income
106 countries[11]. Estimates of case fatality rates after puerperal infection vary from 4 to 50% in
107 Africa and Asia[12].

108
109 Efforts have been made in the last 20 years to standardize definitions of sepsis for the general
110 adult population[13, 14]. In 2016, definitions and clinical criteria for identifying sepsis and
111 septic shock were updated[1] and the Sequential [Sepsis-related] Organ Failure Assessment
112 (SOFA) score was proposed to classify organ dysfunction and thus identify sepsis in the adult
113 population[1]. However, the validity and applicability of the proposed definition and
114 identification criteria to pregnant women are uncertain.

115
116 The objective of this paper is to report the development of a standard definition for maternal
117 sepsis based on a systematic review of literature and a technical consultation.

118
119 **Materials and Methods**

120 The development of a consensus definition of maternal sepsis was based on two components,
121 a systematic review of literature and a technical consultation.

122
123 Systematic review

124 The systematic review of literature focused on definitions and identification criteria of
125 maternal sepsis. Prognostic literature, including articles on prediction scores used to identify
126 obstetric patients at risk of developing complications, were not included in this review.

127
128 *Search Strategy*

129 We conducted an electronic search to identify review articles on maternal sepsis and original
130 articles reporting on the development and testing of maternal sepsis definitions or

131 identification criteria for maternal sepsis. Clinical guidelines and WHO documents related to
132 the prevention, identification and management of maternal sepsis were also reviewed. The
133 literature search in PubMed/MEDLINE and EMBASE databases was carried out on 15/02/2016
134 and included papers published from 01/01/2010 and 15/02/2016. The search strategy used a
135 combination of the following terms, expanded and adapted for each database: “sepsis”,
136 “septicemia”, “septic shock”, “maternal”, “mother”, “pregnancy”, “childbirth”, “postpartum”,
137 “death”, “mortality”, “severe morbidity”, “critical illness”, “near-miss”, “intensive care”,
138 “critical care”, “emergency”, “definition”, “identification criteria”, and “diagnostic criteria”.
139 Additional details of the search strategy are provided in the Supplementary Table S1.
140 Guidelines and WHO documents related to the prevention, identification and treatment of
141 maternal sepsis were searched using the terms “maternal sepsis” and “guideline” in the
142 following databases: National Guideline Clearinghouse, WHO guidelines repository, Guidelines
143 International Network (G-I-N), Institute for Health and Care Excellence (NICE) and Google. Only
144 the first ten pages of results provided by the Google search engine were screened.

145

146 *Review Process*

147 All citations identified through PubMed/MEDLINE and EMBASE were downloaded into
148 reference management software and duplicates were removed. All titles and abstract were
149 screened by two independent reviewers (VNP, MJR), using the following standardized inclusion
150 criteria: (a) all review articles related to maternal sepsis; (b) all articles that report on the
151 development/testing of identification criteria for maternal sepsis cases; (c) all guidelines
152 reporting a definition or identification criteria for maternal sepsis; (d) published in the period
153 2010-2016.

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155 Full-texts of the reviews with potentially relevant information on maternal sepsis, or when
156 title/abstract was deemed insufficient for decision on inclusion/exclusion, were obtained. Full

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157 texts of potential eligible articles were assessed independently by two reviewers (VNP, MJR).
158 WHO documents and guidelines were assessed by one reviewer (MB). Data were extracted
159 using a standardized spreadsheet specifically developed for this review and including the
160 following domains: ‘first author’s name’; ‘year of publication’; ‘study design’; ‘definition of
161 maternal sepsis provided’; ‘list of identification criteria of maternal sepsis provided’. Data was
162 extracted once and extraction forms were double checked by a second reviewer. Discrepancies
163 on inclusions and/or data extraction were resolved through discussion or, if required, by a
164 third reviewer.

165

166 *Data Collection and Synthesis*

167 The definitions of maternal sepsis reported by the included studies, WHO documents and
168 guidelines were extracted. Identification criteria were organized based on organ system
169 involved (circulatory, respiratory, central nervous, renal, coagulation, digestive, skin, genital,
170 and inflammatory). Information concerning specific clinical values or general symptoms and
171 signs was also extracted. No meta-analysis was performed due to the non-numerical nature of
172 the data and heterogeneity.

173

174 Expert consultation

175 Based on the systematic review presented in this paper and the recently published Sepsis-3
176 consensus definition[1], a technical group developed draft definitions of maternal sepsis and
177 proposed a two-stage approach to identify women with possible severe maternal infection
178 who may benefit from prompt clinical action (e.g. further clinical or laboratory investigation,
179 initiation of therapy, and referral), and a second set of criteria to confirm diagnosis of maternal
180 sepsis.

181

182 An online survey was carried out to assess expert opinion on the new definition of sepsis
183 proposed for the adult population (SEPSIS-3) and the alternatives developed by the technical

184 group, the applicability for the obstetric population and the merits of various criteria for the
185 identification of maternal sepsis.
186
187 The survey was sent in March 2016 to 231 experts selected from professional societies of
188 obstetrics, midwifery, nursing and intensive care, research groups working on maternal
189 morbidity and authors of reviews identified in the systematic review describe above. Two
190 reminders were sent to all participants. The survey was anonymous and structured with
191 multiple choice and open-ended questions. Participants were asked to choose a preferred
192 definition of maternal sepsis among various different alternatives drafted by the technical
193 group. The respondents were also asked to provide their level of agreement with the
194 definition of organ dysfunction in adults and its application to maternal sepsis (in a five-point
195 Likert scale ranging from strongly disagree to strongly agree with the statement, , and to rank
196 variables to be used as identification criteria . Combined percentages were calculated for the
197 responses “Strongly agree”and “Agree”, “Strongly disagree”and “Disagree”, “Important” and
198 “Very important”, “Not important” and “Slightly important”.
199
200 In April 2016, WHO’s Department of Reproductive Health Research and Jhpiego convened a
201 face-to-face expert consultation, including some of the experts who participated in the online
202 survey, to review results of this systematic review and online consultation, and to agree on a
203 consensus definition for maternal sepsis.

205 **Results**

206 *Systematic review*

207 The search yielded to 245 citations after exclusion of duplicates. A total of 78 were selected for
208 full-text evaluation. After screening, 26 studies[2, 4-6, 8, 10, 15-35], 9 guidelines[11, 36-43]
209 and 3 WHO documents[44-46] matched the inclusion criteria (Figure 1).

210

211 **<Figure 1 HERE> Figure 1 Flow chart**

212

213 This review found several definitions and sets of criteria being used to identify maternal sepsis
214 cases (Table 1 and 2). However, a substantial proportion of studies (11/26) and guidelines
215 (7/9) referred to the First (1991) or Second (2001) International Consensus on Sepsis
216 developed by a joint task force of American and European societies of intensive care medicine
217 (Table 1). These international consensus published in 1992[47] and 2003[48], proposed
218 definitions and criteria for the identification of sepsis cases in the general population and were
219 based on the previous understanding of sepsis as an infection with a systemic inflammatory
220 response (SIRS).

221

222 **<TABLE 1 HERE> Table 1. Summary of definitions used to refer to maternal sepsis in studies,
223 guidelines and WHO documents included in the systematic review**

224

225

226 Nine studies (9) referred to a previous WHO definition of “puerperal sepsis” as an infection of
227 the genital tract occurring at any time between the onset of rupture of membranes or labour
228 and the 42nd day postpartum, without any reference to complicated infections and systemic
229 response. Another WHO document[45] gives a slightly different definition of puerperal sepsis
230 as any bacterial infection of the genital tract which occurs after the birth of a baby. The most
231 recent WHO documents[45] also provides a definition of septic abortion as an abortion
232 complicated with infection of the genital-tract. However these two documents also included
233 shock or septicemia as one of the clinical presentations that may also occur with infection
234 during the puerperium or after an abortion.

235

236 **TABLE 2 HERE> Table 2. List of criteria used to identify maternal sepsis in studies and
237 guidelines included in the systematic review**

238

239 Coverage of the different stages of pregnancy and the postpartum/post-abortion periods is not
240 consistent. The majority of reviews and guidelines cover all stages of pregnancy, intrapartum,
241 postpartum and post-abortion periods. However some studies[2, 4, 6, 15, 17, 25, 35] and
242 guidelines [36] were limited to certain stages (e.g. postpartum) or conditions (abortion) [2, 15,
243 19, 27]. Furthermore, time limits for the postpartum period varied to up to the end of the 10th
244 day after childbirth or abortion in ICD-10, to the 42nd day postpartum.

245

246 There is also variation regarding the type of infection considered. Nine of the reviews referred
247 to any pregnancy or non-pregnancy-related infection, including incidental infections. Other
248 preferred to differentiate those infections from nosocomial infections, or to classify infections
249 into those related to the genital-tract infections and non-genital-tract infections. Furthermore,
250 four documents (2 reviews[4, 25], 2 WHO documents[44, 45]) limited to postpartum genital
251 tract infections. Three reviews focused on Group A *Streptococcus* (GAS) infections [6, 23, 49].

252

253 Criteria proposed to identify maternal sepsis also vary widely. The most common variables
254 were temperature, heart rate, blood pressure, respiratory rate and leukocytosis. Reviews and
255 guidelines considering laboratory findings for identification of septic women include several
256 testing of liver (enzymes, bilirubin), kidney (creatinine) and clotting (INR, aPPT) function. Five
257 reviews [6, 8, 19, 28, 49] recommended use of cultures to identify causative microorganism,
258 including two reviews specific on GAS infection[6, 49] and requiring isolation of the pathogen
259 for confirmation of diagnosis. Most of the guidelines also referred to the use of glucose, CRP
260 and plasma procalcitonin. These variables were less frequently proposed in the included
261 reviews. The full set of results of the online survey is presented in Supplementary tables S2A,
262 S2B and S3A, S3B.

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264 *Expert consultation*

265 The online survey of experts elicited 48 responses. The full set of results of the online survey is
266 presented in Supplementary S4. The background of the participants was obstetrics (n=23),
267 midwifery (3), adult or obstetric critical care (10), infectious disease (3), researchers (17) and
268 public health specialists (1), from both public (43) and private (5) sector, and representing all
269 regions (Africa (9), Americas (14), Asia (7), Europe (11), Middle East (2)).

270

271 The majority of experts stated that the definition of organ dysfunction used in maternal sepsis
272 should be adapted from the SEPSIS-3 consensus for adults (33/46), and should be based on
273 specific criteria for the obstetric population (35/46). Most of the respondents stated that the
274 assessment of organ dysfunction should include respiratory, cardiovascular, renal and
275 neurologic variables (43, 44, 41 and 38 respondents respectively out of 46 respondents to the
276 questions). Less than half considered important to include fetal variables (22/46). Regarding
277 specific variables, experts tended to prefer thresholds adapted to the obstetric population
278 over those of the qSOFA. Experts also preferred the use of clinical signs over laboratory
279 investigations necessary to calculate the SOFA score. However, two-thirds of the respondents
280 considered serum creatinine (31/44), serum lactate (29/44) and arterial pH (30/44) as
281 important markers of clinical severity. Fourteen of these experts also participated in the face-
282 to-face meeting, where all findings were reviewed and discussed.

283

284 **Consensus Definition of Maternal Sepsis**

285 As a result of this systematic review and international expert consultation, a standard
286 definition of maternal sepsis was proposed as: “Maternal Sepsis is a life-threatening condition
287 defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-
288 abortion, or post-partum period”.^[50]

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290 It is proposed that the identification of organ dysfunction takes place in two steps, one for
291 identification of women with possible severe maternal infections, and presenting with early
292 signs of infection with systemic repercussion (to allow initiation of timely treatment) and
293 another for “confirmed” cases of maternal sepsis (to enable comparative studies). The
294 attributes of these identification criteria were also agreed by the experts. These criteria should
295 be actionable, simple to obtain, able to predict early signs of sepsis, based on clinical signs at
296 bedside, allow for additional tests where available, and suited to high- and low-resource
297 settings. They have to be useful in clinical practice to identify women who may benefit from
298 early intervention. They also have to be compatible with the current classification of disease
299 ICD-10 and contribute to the ongoing revision of the classification to allow comparability of
300 data.

301
302 **Discussion**

303 This paper describes the process towards a consensus definition of maternal sepsis, based on a
304 systematic review and international expert consultation. This new WHO definition of maternal
305 sepsis may facilitate a better understanding of the burden of this condition and allow
306 comparisons across different settings. Ultimately this will provide the basis for effective
307 prevention, identification and management of maternal sepsis.

308
309 The systematic review showed a wide range of definitions and criteria being used to describe
310 maternal sepsis. Most of the reviews and guidelines identified align with the previous
311 definitions of sepsis, severe sepsis and septic shock, and criteria used to identify adult septic
312 patients. However, in obstetrics, the term sepsis is often used interchangeably to refer to
313 puerperal infectious morbidity. There are also differences in the type of infections considered.
314 Some definitions included only infections from the genital tract (chorioamnionitis,
315 endometritis [22]), while others have a broader definition and include infections from other

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316 organ systems, such as pneumonia, or incidental infections (malaria). In addition, few studies
317 report maternal sepsis across all the spectrum of pregnancy, including antenatal, postpartum,
318 and abortion related sepsis. All these variations may have important implications for clinical
319 care and potentially lead to misdiagnosis, inadequate treatment or delays in care. They also
320 have epidemiological implications, making it difficult to assess the real burden of maternal
321 sepsis and allow comparisons across different settings (hospitals, countries).

322
323 In February 2016 the Third International Consensus on Sepsis was published and included a
324 substantial change in the understanding of sepsis[1]. This Sepsis-3 consensus definition
325 defined sepsis as a life-threatening organ dysfunction caused by a dysregulated host response
326 to infection. The significance of the systemic inflammatory response was de-emphasized
327 compared to the previous definition based on the SIRS criteria. The SOFA score was also
328 introduced to better describe severity of organ dysfunction and to predict in-hospital
329 mortality^[1]. This scoring includes the evaluation for the following organ systems: Respiration
330 (PaO₂), Coagulation (platelets), Liver (bilirubin), Cardiovascular (mean arterial blood pressure,
331 MAP), Central Nervous System (Glasgow Coma Scale), Renal (serum creatinine and urine
332 output).

333
334 The proposed new WHO definition of maternal sepsis aligns with the current understanding of
335 sepsis in adults, and considers sepsis as a consequence of a dysregulated, life-threatening
336 response to infection. This is supported by the results of the expert consultation, but also
337 previous guidelines which already were recommending the use of definitions and criteria
338 developed for the general population. However, many of the variables used to calculate the
339 SOFA score were not mentioned in the included reviews or supported by results of the expert
340 consultation. This is despite the fact that the SOFA score variables and its clinical proxies have
341 been previously proposed by WHO as gold-standard for severity markers to be used to identify

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342 women with life-threatening conditions[51]. For example PaO2 was mentioned in two reviews
343 only [15, 17]. Glasgow Coma scale was not mentioned in any of the included reviews and in
344 one guideline only[42]. Results of the online survey showed similar results, as most of the
345 experts preferred to use clinical markers of severity over laboratory investigation necessary to
346 compute the SOFA score. The exception was the use of serum creatinine and lactate. These
347 results may be in part influence by the criteria set in the survey, such as ensuring applicability
348 in low resource settings, in a wide range of clinical settings and by different cadres of health
349 care providers. The results also suggest that the list of identification criteria used for maternal
350 sepsis must accommodate different resources available to clinicians, whilst allowing them to
351 incorporate into the diagnosis laboratory findings when available.

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353 The new definition also aligns with the WHO definition of maternal morbidity defined as “any
354 health condition attributed to and/or complicating pregnancy and childbirth that has a
355 negative impact on the woman’s wellbeing and/or functioning”[52]. Regarding infectious
356 morbidities, the definition of pregnancy related infections includes genital tract infections (e.g.
357 chorioamnionitis and endometritis), extra-genital infections (e.g. mastitis, breast abscess,
358 pyelonephritis, tetanus), as well as other maternal infections complicating pregnancy,
359 childbirth and the puerperium (e.g. HIV, malaria, STIs, other fungal and viral infections).

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361 A clear problem for using clinical criteria for pregnant women is that physiological changes in
362 pregnancy may affect many organ systems: blood pressure, PaO2, bilirubin or creatinine
363 measurements [3]. Furthermore, experts report that clinical criteria must be applied with great
364 care in the obstetric patient where, sometimes, only one or even none of the above findings
365 are present despite a severe infection [4]. For this reason modified obstetric early warning
366 scoring systems (MOEWS) have been developed for pregnant women[53]. MOEWS systems
367 vary widely in terms of alert thresholds, format, and accuracy. However, none of the current

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368 existing tools have shown good performance in predicting the development of severe sepsis
369 [53] [54]. A limitation of this review is that we did not include these MOEWS or SOS (Sepsis in
370 Obstetrics) scores as potential sources of criteria for identification of septic women. However,
371 these scores have not been prospectively validated in a large obstetric population across
372 different settings, particularly in low- and middle-income countries where their impact could
373 be the largest.

374

375 **Conclusion**

376 The new maternal definition and set of identification criteria will be tested and validated in a
377 large global study[55]. A global one-week cross-sectional study will be carried out in 2017 in a
378 large network of health facilities, the *Ending Maternal Sepsis Week* study. This study aims to
379 cover existing knowledge gaps. It will assess the frequency of maternal sepsis using the
380 proposed definition and identification criteria in all settings, particularly in low- and middle-
381 income countries, and across the spectrum of pregnancy including the antenatal, peripartum,
382 postpartum and post-abortion periods. Information on prevention and management strategies
383 will be collected to inform the development of a strategy for reducing maternal infections and
384 sepsis.

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394 **Table 1. Summary of definitions used to refer to maternal sepsis in studies, guidelines and**
 395 **WHO documents included in the systematic review**

Name of organization proposing the definition, (year)	Definition	Studies referring to the definition	Guidelines referring to the definition
American College of Chest Physicians and the Society of Critical Care Medicine (1992)	<p><i>Systemic inflammatory response syndrome (SIRS):</i> Widespread inflammatory response to severe clinical insult defined by the presence of two or more of the following symptoms:</p> <ul style="list-style-type: none"> ▶ Temperature >38°C or <36°C ▶ Heart rate >90/min ▶ Respiratory rate >20/min or PaCO₂ <32 mm Hg ▶ White blood cells >12×10⁹/dL or <4×10⁹/dL or >10% immature forms <p><i>Sepsis:</i> SIRS plus definitive evidence of infection</p> <p><i>Severe sepsis:</i> Sepsis with signs of organ dysfunction, hypoperfusion or hypotension</p> <p><i>Septic shock:</i> Sepsis with hypotension despite adequate fluid resuscitation</p>	Barton, 2012[8]; Buddeberg, 2015[4]; Chebbo, 2016[17]; Cordioli, 2013; Frise, 2015[21]; Morgan, 2013[5]; Oud[33] Pacheco, 2014[34]; van Dillen, 2010[10]	FLASOG 2013[43]
International Classification of Diseases, Revision 10 (ICD-10) (1994)	A temperature rise above 100.4 F (38 °C) maintained over 24 h or recurring during the period from the end of the first to the end of the 10th day after childbirth or abortion.	Acosta, 2013[2]; Bamfo, 2013[16]; Dillen, 2010[10]; Hashmi, 2014[24]; Sung, 2011[56]	-
SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference (2001)	Refers to American College of Chest Physicians and the Society of Critical Care Medicine (1992) with expanded list of criteria.	Arulkumaran, 2013[15]; Hashmi, 2014[24]	CEC 2015[41]; HSE 2014[39]; NICE 2016[38]; South Australian Perinatal Practice Guidelines 2014[40]; RCOG 2011[37]; RCOG 2012[11]
The prevention and management of puerperal infections World Health Organization (WHO) (1992)	<i>Puerperal sepsis</i> is an infection of the genital tract occurring at any time between the rupture of membranes or labour and the 42nd day postpartum, in which, two or more of the following are present: pelvic pain, fever, abnormal vaginal discharge and delay in the reduction of the size of the uterus	Acosta, 2013[2]; Buddeberg, 2015[4]; Bamfo, 2013[16]; Karsnitz, 2013[25]; Lamy[27] Lucas, 2011[29]; Dillen, 2010[10]; Hashmi, 2014[24]; Sung, 2011[56]	-
Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors WHO (2003)	Infection can result in failure of the circulatory system to maintain adequate perfusion of the vital organs (shock). Suspect or anticipate shock if at least one	-	WHO 2003[46]

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	<p>of the following is present: fast weak pulse (110 per minute or more), low blood pressure (systolic less than 90 mmHg), sweatiness or cold clammy skin, rapid breathing (rate of 30 breaths or more), anxiousness, confusion or unconsciousness, scanty urine output (less than 30 ml per hour), other symptoms and signs of shock include: pallor (specially of inner eyelid, palms or around mouth).</p> <p>Septic abortion: an abortion complicated with infection. Sepsis may result from infection if organisms rise from the lower genital tract following either spontaneous or unsafe abortion. Symptoms and signs are: lower abdominal pain, rebound tenderness, tender uterus, prolonged bleeding, malaise, fever, foul-smelling vaginal discharge, purulent cervical discharge, cervical motion tenderness</p>		
<p>Midwifery education modules – Managing puerperal sepsis (WHO) (2008)</p>	<p><i>Puerperal sepsis</i> is any bacterial infection of the genital tract which occurs after the birth of a baby. The following symptoms and signs occur in puerperal sepsis: fever (temperature of 38°C or more), chills and general malaise, lower abdominal pain, tender uterus, subinvolution of the uterus, purulent, foul-smelling lochia. Symptoms and signs that may also be present: light vaginal bleeding, shock</p> <p><i>Septic abortion</i>: An abortion (loss of pregnancy during the first 22 weeks) that is followed by infection of the uterus and may spread throughout the genital tract causing fever and chills, foul-smelling vaginal discharge, pelvic pain and septicaemia</p>	-	<p>WHO 2008[45]</p>

396 ACCP = American College of Chest Physicians, ATS = American Thoracic Society, ESICM = European Society of
397 Intensive Care Medicine, SCCM = Society of Critical Care Medicine, SIS = Surgical Infection Society

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Table 2. List of criteria used to identify maternal sepsis in studies and guidelines included in the systematic review

System	Variable	Values or ranges (min - max)	References studies	References guidelines	Other signs	Other symptoms
Circulatory	Heart rate	> 90 /min (90-120/min) or > 2 SD above the normal value for age	[2, 4, 5, 8, 10, 15-18, 21, 23-25, 27, 29, 30, 32-34]	[11, 14, 36, 38-42]	Vasoplegia[31]	-
	Blood pressure	SBP <100 mm Hg MAP <70 (65-70) mm Hg Decrease SBP >40 mm Hg	[4, 10, 15, 17, 18, 23, 25, 27, 33, 34]	[11, 14, 36, 38, 40-42]	Hypotension[23], significant oedema / positive fluid balance[10, 15, 18, 33, 34, 39, 43]	-
Respiratory	Respiratory rate	>20 / min (≤ 10 or ≥ 25 / min)	[2, 4, 5, 8, 10, 16, 21, 24, 27, 30, 32-35]	[11, 14, 36, 38, 40-42]	Marked tachypnea, Acute lung injury in the absence of pneumonia as infection source, Arterial hypoxaemia [10, 17, 24, 34, 49]	Cough, sore throat[4, 20], chest pain[37]
	Arterial hypoxaemia	PaO2 (arterial oxygen partial pressure) /FIO2 (fraction of inspired oxygen) <40kPa	-	[39]		
Central Nervous System	Altered mental status	Glasgow Coma scale <14/15	-	[42]	Confusion, decreased alertness, prostration, unduly anxious, distressed or panicky[4, 11, 19, 20, 36-43]	Headache, pain, lethargy, body pain, arthralgia, myalgia[4, 19, 20, 25]
	Hyperthermia	> 38 °C (37.8-38.5 °C)	[2, 4, 5, 8, 10, 15-18, 21, 23-25, 27, 29-34]	[11, 14, 36, 39-42, 45]	-	Fever, Chills[23, 25, 29]
	Hypothermia	< 36 °C (35.5 °C - 36 °C)	[2, 4, 5, 8, 10, 15-18, 21, 24, 25, 27, 29, 31-34]	[11, 36, 39-41]	-	-
Renal	Lactate (mmol/L)	>1 (>1-4)	[6, 10, 15, 17, 18, 20, 33]	[11, 14, 36, 38, 39, 41]	Acute oliguria, anuria[8, 10, 15, 17, 19, 20, 24, 33, 34]	Urinary symptoms[4, 20, 22], renal angle pain and tenderness [37]
	Kidney (Creat mg/dL)	> 2 mg/dL or Raise > 0.5 mg/dL	[6, 10, 15, 17, 18, 20, 24, 33]	[34,37,40,42]		
Coagulation	Platelets (/ml)	<100,000	[6, 10, 15, 17, 18, 33]	[11, 36, 37, 39, 42]	-	Coagulopathy, Disseminated intravascular coagulation[6, 31, 35, 49]
		INR >1.5 or aPTT >60 s	[10, 15, 17, 18, 20, 24, 33]	[11, 36-40, 42, 43]		
Digestive	Glucose (mmol/L)	> 7.7 in the absence of DM	[10, 15, 17]	[11, 14, 36, 39, 40]	Mild intestinal tenderness without rebound tenderness	Reduced appetite, Nausea, Vomiting,
	Liver: total	> 2 mg/dL	[6, 10, 15, 17, 18,	[11, 36-40, 43]		

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	bilirubin (mmol/L)	> 70mmol/L	20, 24, 33]		Peritonitis[4, 20, 22, 25] Ileus[10, 15, 17, 18, 33, 34]	diarrhea, abdominal pain[4, 8, 20, 22, 27]
Skin	-	-	-	-	Decreased capillary refill, clammed or mottled skin Generalized erythematous macular rash, Rash, erythema[4, 23, 49] Necrotizing fasciitis or myositis Gangrene[6, 8, 10, 15, 17, 18, 22, 33-35, 49]	-
Genital	-	-	-	-	Pus or foul-smelling fluid from the cervix, pyometra, cervicitis, metrorrhagia, delay in the rate of reduction of size of uterus [8, 16, 19, 22, 23, 25, 27]	Purulent vaginal discharge[25, 27] pelvic pain, [8, 16, 19, 22, 23, 25]
Inflammatory	WBC(cells/ μ l)	>12000 (11000-16000) or <4000 or >10% immature forms	[2, 4, 5, 8, 10, 15-18, 20, 21, 23-25, 29, 31-34]	[11, 36-43]	Preterm labour[20]	Breast redness, Pain of site of infection[4, 8, 17, 20]
	CRP	> 7mg/L > 2SD	[10, 15, 17, 18, 24, 33]	[11, 36-40, 43]		
	Procalcitonin	> 2SD	[15, 17, 18, 33]	[39, 43]		
Other	Culture	Positive	[6, 8, 19, 28, 49]	-	-	-
	Fetal distress	-	-	-	Fetal distress secondary to maternal acidosis[41]	Reduced or absent fetal movements[41]

CRP: C-reactive protein; MAP: Mean Arterial Blood Pressure; SBP: Systolic Blood Pressure; WBC: White Blood Cell Count.

List of abbreviations

1		
2	ACCP	American College of Chest Physicians
3		
4	aPPT	Activated Partial Thromboplastin Time
5		
6	ATS	American Thoracic Society
7		
8	CRP	C-reactive protein
9		
10	ESICM	European Society of Intensive Care Medicine
11		
12	GAS	Group A Streptococcus
13		
14	G-I-N	Guidelines International Network
15		
16	ICD-10	International Classification of Disease, version 10
17		
18	INR	International Normalized Ratio
19		
20	MAP	Mean Arterial Blood Pressure
21		
22	MOEWS	Modified Obstetric Early Warning Scoring Systems
23		
24	NICE	Institute for Health and Care Excellence
25		
26	PaO ₂	Oxygen Partial Pressure
27		
28	qSOFA	quick SOFA
29		
30	SBP	Systolic Blood Pressure
31		
32	SCCM	Society of Critical Care Medicine,
33		
34	SIS	Surgical Infection Society
35		
36	SOFA	Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score
37		
38	SOS	Sepsis in Obstetrics
39		
40	WBC	White Blood Cell Count
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42	WHO	World Health Organization
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Declarations

Ethics approval and consent to participate

The completion of the online survey implied participant consent to participate

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files.

Competing interests

The authors declare that they have no competing interests

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Author Contributions

MB, VNP, JPS and AMG conceptualized the study; VNP and MJR carried out screening, data extraction and analyzed results of the systematic review. MB and JPS contributed to the analysis of the systematic review and coordinated and reviewed results of the expert consultation. AC and DL contributed to the conceptualisation of the international consultation and analysis of the result. MB, VNP, MJR, drafted the paper. All authors commented on and approved the final manuscript.

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9 **Supporting information**

10 Supplementary table 1. Search strategy.

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13 Supplementary tables 2A and 2B. Summary of studies included in the systematic review:
14 definitions and identification criteria for maternal sepsis.
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17 Supplementary tables 3A and 3B. Summary of guidelines included in the systematic review:
18 additional symptoms and signs.
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20 Supplementary file S4. Results of the online survey.
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Figure 1 Flow chart

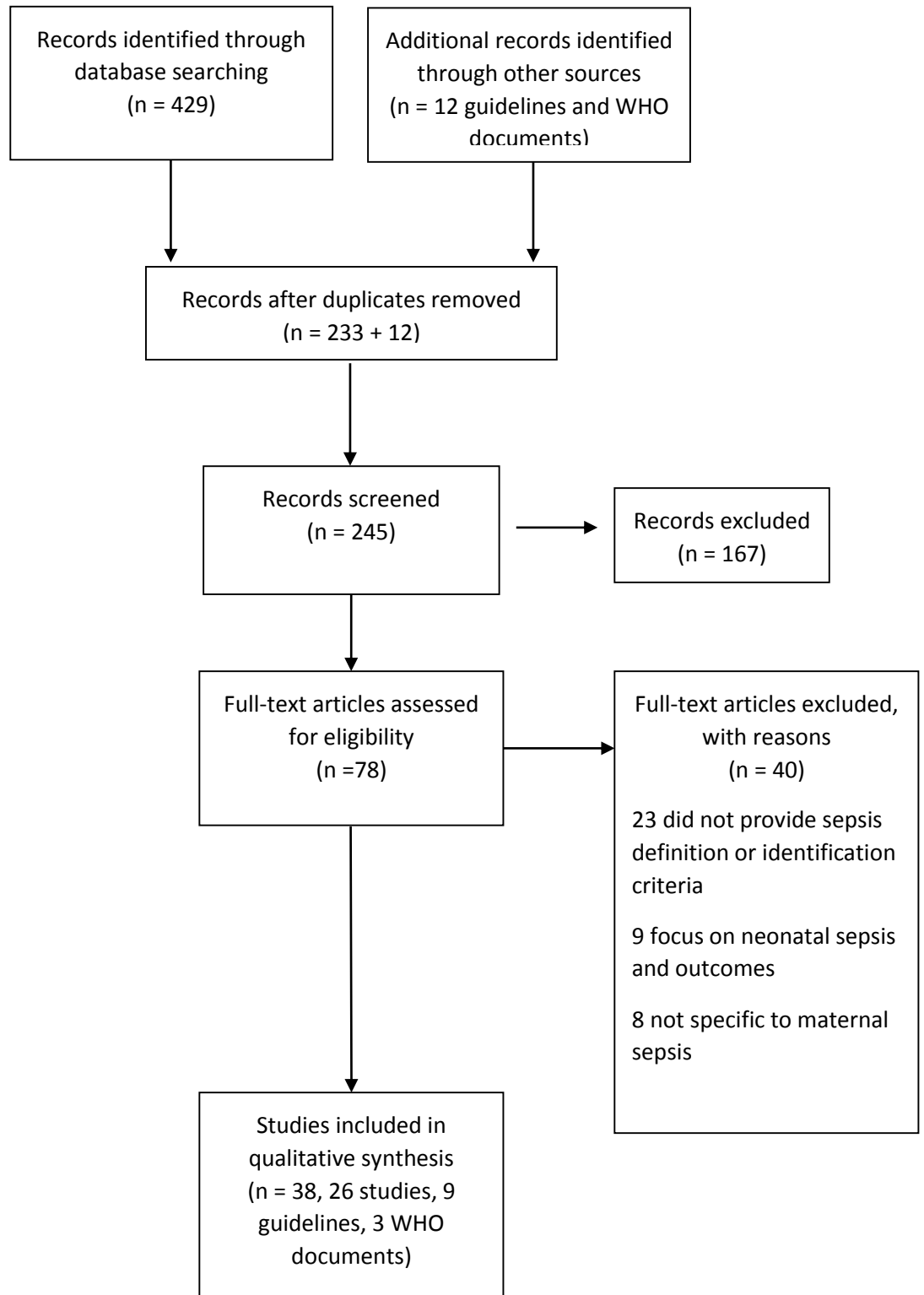
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Identification

Screening


Eligibility

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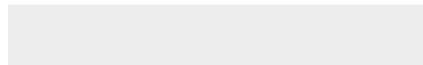


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