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## Maternal and early onset neonatal bacterial sepsis: burden and strategies for prevention in sub-Saharan Africa

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### Abstract

Maternal and child health are high priorities for international development. Through a Review of published work, we show substantial gaps in current knowledge on incidence (cases per live births), aetiology, and risk factors for both maternal and early onset neonatal bacterial sepsis in sub-Saharan Africa. Although existing published data suggest that sepsis causes about 10% of all maternal deaths and 26% of neonatal deaths, these are likely to be considerable underestimates because of methodological limitations. Successful intervention strategies in resource-rich settings and early studies in sub-Saharan Africa suggest that the burden of maternal and early onset neonatal bacterial sepsis could be reduced through simple interventions, including antiseptic and antibiotic treatment. An effective way to expedite evidence to guide interventions and determine the incidence, aetiology, and risk factors for sepsis in sub-Saharan Africa would be through a multiarmed factorial intervention trial aimed at reducing both maternal and early onset neonatal bacterial sepsis in sub-Saharan Africa.

### Introduction

Millennium development goals (MDGs) four and five identify maternal and child health as high priorities for international development.<sup>1</sup> The greatest unmet need is in sub-Saharan Africa,<sup>2,3</sup> accounting for half of all maternal and child deaths worldwide. In all the countries reported in sub-Saharan Africa, except Eritrea, insufficient or no progress in reducing child mortality has been made between 1990 and 2005 to achieve MDG four (a two-thirds reduction in childhood mortality rates between 1990 and 2015).<sup>4</sup> Equivalent longitudinal data on maternal mortality to identify progress towards MDG five (a reduction in the maternal mortality ratio by three-quarters between 1990 and 2015) is unavailable. However, maternal mortality (measured as maternal mortality ratio) remains high or very high.<sup>4,5</sup> Maternal mortality ratio is defined as the annual number of female deaths from any cause related to or aggravated by pregnancy or its management (excluding accidental or incidental causes) during pregnancy and childbirth, or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, for a specified year.<sup>2</sup> In 2005, WHO estimated the maternal mortality ratio as 900 per 100 000 live births in sub-Saharan Africa, 100-times the maternal mortality ratio of resource-rich countries (nine per 100 000 live births).<sup>2</sup> The neonatal mortality rate—defined as the number of babies dying in the neonatal period (first 28 days of life) per 1000 live births<sup>6</sup>—was estimated as 44 per 1000 live births, four times the rate in Europe (11 per 1000 births) and the Americas (12 per 1000 births).<sup>6</sup> Of these neonatal deaths, three-quarters occur early (within 7 days of birth). Additionally, stillbirths are thought to equal the number of neonatal deaths worldwide.<sup>6</sup>

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Conflicts of interests

We declare that we have no conflicts of interest.

This Review aims to describe the burden of sepsis contributing to maternal and early onset neonatal morbidity and mortality in sub-Saharan Africa, and the evidence for potential interventions. The close relationship between mothers and their infants results in shared aetiologies and risk factors for infectious diseases, HIV being the most recently highlighted.<sup>7-10</sup> In resource-rich countries, interventions such as risk-based antibiotic prophylaxis (based on microbiological screening or risk factors in pregnancy) have been highly effective in reducing both early onset neonatal bacterial<sup>11</sup> and maternal sepsis.<sup>12</sup> Consequently, 15% of all neonatal deaths in countries with low neonatal mortality rates (less than five per 1000 live births in countries such as the UK and USA) are from infection, diarrhoea, or both, but 34% of all neonatal deaths in countries with high neonatal mortality rates (more than 44 per 1000 live births in countries such as the Democratic Republic of Congo and Nigeria) are from these causes.<sup>13</sup>

Current research in resource-rich countries aims to further reduce neonatal sepsis through the development of maternal vaccines against prevalent pathogens, such as *Streptococcus agalactiae* (group B streptococcus).<sup>14</sup> However, in sub-Saharan Africa research has generally focused on either child or maternal health, and there are likely to be opportunities for simple preventive measures affecting both. These could be based on improving health systems and new approaches identified through improved epidemiology and subsequent intervention trials.

Given the very high maternal and neonatal mortality rates in sub-Saharan Africa, and the effectiveness of simple interventions to prevent maternal and early onset neonatal bacterial sepsis shown elsewhere, identifying research priorities and developing strategies to prevent maternal and early onset neonatal bacterial sepsis in sub-Saharan Africa is essential.

## Incidence of maternal sepsis

WHO defines puerperal sepsis as infection of the genital tract occurring at any time between the onset of the rupture of membranes or labour and the 42nd day post partum in which fever and one or more of the following are present: pelvic pain, abnormal vaginal discharge, abnormal odour of discharge, and delay in the rate of reduction of size of the uterus.<sup>15</sup> The term maternal sepsis is used in this Review to include all infections in the same period.

Most estimates of puerperal sepsis in sub-Saharan Africa come from retrospective studies of maternal deaths, without microbiological investigation. Thus, these data reflect the burden of clinically defined puerperal sepsis as a cause of death, rather than the actual incidence (cases per live births) of puerperal sepsis or other important infections in the population.

A 2006 WHO systematic review of the causes of maternal deaths worldwide<sup>16</sup> estimated that 9.7% (95% CI 6.3–12.6) of maternal deaths in Africa were due to puerperal sepsis. The datasets (since 1990) were selected to be representative of their populations and selected by methodological quality against predetermined criteria. Nine studies from Africa were included, and eight of these were from sub-Saharan Africa. All concerned a single country or region, retrospectively reviewing maternal deaths,<sup>17-23</sup> except one, which was a multinational, prospective, population-based study in six countries in west Africa recruiting and following up 19 545 pregnant women.<sup>24</sup> In this study, maternal deaths were followed up by analysis of medical records and by verbal autopsy. Six maternal deaths were attributed to sepsis, accounting for 10.9% of all maternal deaths or 33.9 (12.4–73.8) deaths per 100 000 live births.<sup>24</sup> The wide CIs reflect the difficulty of using maternal death as a prospective outcome, even in a multinational study. Retrospective case reviews, however, are hampered by poor documentation and limited investigations, which reduce the accuracy of these reports. Many maternal deaths are unrecorded, particularly if delivery occurs outside of a hospital.

Since the WHO systematic review, a South African confidential enquiry<sup>25</sup> into maternal deaths (representative of the population it described) reported puerperal sepsis as the cause of 8.3% (274) of deaths (2002–04). The diagnosis of puerperal sepsis was separated from non-pregnancy related infections, which accounted for 23.0% (130) of maternal deaths in 1998,<sup>21</sup> increasing to 37.8% (1246) of maternal deaths in 2002–04.<sup>25</sup> Of these deaths, 53.1% (662) were attributed to HIV/AIDS, 25.4% (316) to pneumonia, 8.3% (104) to tuberculosis, and 6.3% (79) to meningitis. Diagnoses were clinical, rather than from systematic microbiological investigation.

An important recent study comes from a tertiary facility in Mozambique;<sup>26</sup> although not population-based (referral centre), it is included here as the first prospective study in sub-Saharan Africa to use autopsy and histology to determine the cause of maternal death. From 139 autopsies, 14 (10.1%) were puerperal or post-caesarean sepsis. Additionally, 67 (48.2%) deaths were from other infectious diseases (table 1). Using the data from this study, a retrospective review has since been carried out to assess the correlation between autopsy (used as gold-standard for cause of death) and prior clinical diagnosis of maternal cause of death. The highest rates of false-negative clinical diagnoses were for infectious diseases, with sensitivities under 50%. Hypertensive disorders (eclampsia) were the main false-positive diagnoses.<sup>36</sup> All of the other studies of maternal mortality described above are based on diagnoses of maternal death from clinical records or verbal autopsy only. Although the study from Mozambique is a single-site tertiary-referral centre and the results cannot necessarily be extrapolated across sub-Saharan Africa, it does suggest that there might be substantial inaccuracies in the available data on causes of maternal mortality, particularly under-reporting of infection as a cause of death.<sup>36</sup>

Data on maternal morbidity in sub-Saharan Africa are very limited. Table 1 summarises those studies providing data on maternal morbidity from puerperal sepsis, or providing microbiological and histological data. These studies mainly comprise retrospective case reviews, facility based studies,<sup>27,28</sup> or studies with substantial missing data.<sup>35</sup> Some of the best evidence comes from the multinational, prospective, population-based study from west Africa, described above,<sup>30</sup> which includes data on maternal morbidity and puerperal sepsis—19 545 women were actively followed up post partum.<sup>30</sup> 18 cases of puerperal sepsis were identified, representing a maternal morbidity ratio of 90 (50–140) per 100 000 live births. The six patients that died represented a case fatality ratio of 33%.

Estimates of the prevalence of maternal sepsis also come from intervention studies. Three clinical trials in sub-Saharan Africa intervened to reduce puerperal sepsis. A single facility-based trial in Malawi<sup>32</sup> used manual antiseptic cleansing of the birth canal at vaginal examination, and wiping of the newborn at delivery. Post partum infection was diagnosed clinically after delivery, or if women re-presented (passive follow-up). Six (5.6%) of 107 women who delivered in the intervention period, compared with 17 (12.7%) of 134 women who delivered in the non-intervention period were diagnosed with puerperal sepsis.

The second study was a double-blind randomised controlled trial in two facilities in Durban, South Africa,<sup>31</sup> among women infected with HIV in whom vaginal delivery was expected. A single dose of intravenous cefoxitin or placebo was given during birth, with follow up for signs of any infectious morbidity at 72 h, 1 week, and 2 weeks. Overall there was no significant difference in symptoms suggestive of puerperal sepsis, although cefoxitin significantly reduced endometritis.

The third study was community-based in ten surveillance sites across two rural districts of Mwanza, Tanzania,<sup>34</sup> involving the provision of a clean delivery kit and maternal education on hygienic delivery. Allocation was dependent on maternal choice rather than

randomisation; puerperal sepsis up to 5 days post partum was diagnosed in 1.1% (19) of women who used the kit and 3.6% (50) who did not.

It is clear that a single, reliable estimate of the incidence of puerperal sepsis in sub-Saharan Africa cannot be made. However, the available evidence suggests that infections around childbirth substantially contribute to maternal morbidity, are underestimated, are a leading cause of death in mothers in sub-Saharan Africa, and are more frequent in hospital-based deliveries than in the community. It is apparent that future studies should look at the morbidity and mortality from both puerperal sepsis and maternal sepsis not thought to be directly related to delivery, and should use adequate microbiological investigations.

## Incidence of early onset neonatal sepsis

Neonatal sepsis, defined as sepsis within the first 28 days of life, is estimated to cause 26% of all neonatal deaths worldwide.<sup>6</sup> Few studies in sub-Saharan Africa differentiate between early and late onset neonatal sepsis and there are variations in the periods used to define early and late.<sup>37</sup> Differentiation is important since early onset neonatal bacterial sepsis is more likely to reflect vertically acquired infection from the maternal genital tract. It therefore has a different aetiology to late onset neonatal sepsis, and potentially different means of prevention. Here, we define early onset neonatal bacterial sepsis as sepsis in neonates less than 7 days old and only include studies with microbiologically confirmed data.

Estimates of the incidence of neonatal sepsis are all from single-facility studies, and vary in their findings (table 2). A study from Malawi<sup>38</sup> is the most specific, considering the incidence of early onset neonatal sepsis caused by *S agalactiae* alone, which was reported as 0.92 cases per 1000 live births.

Regarding neonatal sepsis as a whole, 5.46 cases of neonatal bacteraemia per 1000 live births were recorded in Kilifi, Kenya,<sup>39</sup> through blood-culture surveillance of all hospital admissions (both in-born and out-born neonates). In Nigeria, 6.5 cases of neonatal sepsis per 1000 live births occurring in a referral hospital were recorded.<sup>40</sup> 21 cases of neonatal sepsis per 1000 live births were reported from a referral hospital in Zimbabwe.<sup>41</sup> Maternal deliveries in the Zimbabwean study were described as high risk and likely to result in a higher incidence of neonatal sepsis. Fewer cases (30 of 6630 live births) of neonatal sepsis were identified from community referrals (out-born neonates), but the authors do not calculate an incidence, due to the likelihood of missed cases.<sup>41</sup>

It is difficult to interpret these incidence data; the Zimbabwe<sup>41</sup> and Nigeria<sup>40</sup> single-facility studies considered all live births at that facility and their outcomes, using the number of births at the facility as the denominator to calculate incidence, but these cannot be extrapolated to the general population. The Malawian<sup>38</sup> and Kenyan<sup>39</sup> studies included both in-born and out-born neonates and estimated incidence based on catchment-population data. Their results are minimum estimates, since not all neonates with sepsis will have been referred, and cases of culture-negative sepsis would not be included. The denominators might also be reduced if birth records are incomplete.

Studies with a high proportion of in-born neonates are likely to have a higher proportion of early onset neonatal sepsis, 68% (110) of all neonatal sepsis cases in the Zimbabwe study were early onset.<sup>41</sup> By contrast, community-based studies (including mainly out-born neonates), such as the multicentre WHO collaborative study, from The Gambia, Ethiopia, Papua New Guinea, and the Philippines,<sup>52</sup> might be biased against recording early onset neonatal bacterial sepsis, because babies with severe early-onset infections might die before presentation. Only 30% (25) of neonatal sepsis cases in the WHO Young Infants study<sup>52</sup>

were early onset. Although the WHO study was not population-based, a simple calculation using data from Gambian sites can be made.<sup>42</sup> There were 53 cases of young infant sepsis (infants younger than 90 days) from a catchment area of 12 000 births, which would give an incidence of 4.42 cases of young infant sepsis per 1000 live births (if the study is assumed to simultaneously cover both hospitals for a year, rather than each hospital studied consecutively for a year).

Intervention studies are also typically from single facilities, and therefore not necessarily representative of the population. Rates of admissions due to sepsis dropped immediately after birth canal cleansing was introduced in Malawi, and stayed substantially lower during the intervention period compared with the non-intervention months (7.8 vs 17.9 per 1000 live births).<sup>32</sup> In South Africa, among mothers infected with HIV, a non-significant reduction in neonatal sepsis was also seen in the cefoxitin trial: neonatal sepsis was diagnosed in 1.3% of babies whose mothers received placebo and 0.7% of those whose mothers received cefoxitin.<sup>31</sup> The community-based study in Mwanza<sup>34</sup> considered neonatal sepsis only in terms of cord infection at 5 days. Five infants (0.3%) of women who used the kit and 48 infants of women who did not use the kit (3.9%) developed cord infection.

Estimates of incidence of early onset neonatal bacterial sepsis therefore vary widely, but the available data indicates a high burden of disease. Multisite population-based studies with uniform definitions would improve our understanding of early onset neonatal bacterial sepsis. This is important, since simple interventions reducing the incidence of early onset neonatal bacterial sepsis could be prioritised in health planning.

## Aetiology

There are few microbiological data on puerperal sepsis in sub-Saharan Africa (table 1). A case-control study from Nairobi, Kenya,<sup>33</sup> found a significant difference in the isolation of *Neisseria gonorrhoeae* or *Chlamydia trachomatis* from the endometrium and cervix of women with post-partum endometritis (35 cases) compared with those without (30 cases). Samples were taken at 6 days post partum for the isolation of these organisms and *Mycoplasma hominis*, *Ureaplasma urealyticum* (isolated equally from both cases and controls), and *S agalactiae* (not isolated in either group). A high prevalence (19; 28%) of *N gonorrhoeae* was also reported in cases of puerperal sepsis from a study of pelvic infections in Ethiopia.<sup>29</sup> Another retrospective study from Nigeria,<sup>27</sup> of microbiological isolates from the genital tract of patients with puerperal sepsis (taken for clinical purposes, sites not specified), identified *S aureus* (29; 20%) as the most common pathogen, followed by *Escherichia coli* (18; 12%) and *Proteus* sp (17; 12%). However, there was a low proportion of positive cultures (85 of 146), but there were no facilities for anaerobic culture and again, no growth of streptococcal species. Since these streptococcal species are fastidious organisms, isolation might have been limited by bacteriological facilities.

The aetiology of neonatal sepsis has been more frequently described (table 2), reflecting a recognised need for data to improve treatment guidelines.<sup>53</sup> Before the WHO collaborative study (1990–93) in The Gambia, Ethiopia, the Philippines, and Papua New Guinea the main causative organisms described from non-industrialised countries were *S aureus* and *Klebsiella* sp,<sup>49,52</sup> also reported more recently from Nigeria.<sup>48</sup> The WHO study site in The Gambia used two facilities, including young infant admissions (younger than 91 days) to both a first-referral medical facility and tertiary-centre hospital. 38 infants without meningitis had positive blood cultures, specifically *S aureus* (17 cultures), *Streptococcus pneumoniae* (three), *Salmonella* spp (five), *E coli* (three), other enterobacteriaceae (four), *Streptococcus pyogenes* (group A streptococcus) (three), *S agalactiae* (group B streptococcus) (one), *Moraxella* spp (one), and group G streptococci (one).<sup>42</sup> The Ethiopian

site identified 41 positive cultures in young infants. *S pneumoniae* was common (ten), as were *S pyogenes* (nine) and *Salmonella* spp (five). However, *S agalactiae* was absent. Culture-confirmed cases of meningitis (15) were predominantly caused by *S pneumoniae* (seven).<sup>43</sup>

Recent research has challenged the findings of the WHO Young Infant study, regarding early onset neonatal bacterial sepsis. Bacteriological surveillance of all neonatal admissions in Kilifi, Kenya 1998–2002 identified *S agalactiae* as the most common Gram-positive organism and *E coli* as the most common Gram-negative organism isolated in neonates younger than 7 days.<sup>37</sup> These findings are supported by data from Blantyre, Malawi,<sup>38,44</sup> and from other single-facility studies in Kenya,<sup>45,47</sup> Zimbabwe,<sup>41</sup> and South Africa<sup>46</sup> (table 2).

The disparity in *S agalactiae* is likely accounted for by study design. The WHO Young Infants study, like a Nigerian study,<sup>50</sup> focused on outpatient referrals rather than in-born neonates. Severe, rapidly fatal, early onset neonatal bacterial sepsis was therefore probably under-represented compared with facility-based studies, because of the time needed to seek medical facilities. The newer findings are of particular note since *S agalactiae* infections have been substantially reduced with antibiotic-based prevention strategies in resource-rich countries. For example, chemoprophylaxis in the USA has reduced the incidence of early onset neonatal bacterial sepsis caused by *S agalactiae* from 1.7 per 1000 live births in 1993 to 0.6 per 1000 in 1998.<sup>11</sup>

Our knowledge of the aetiology of maternal sepsis is limited compared with our growing understanding of the aetiology of neonatal sepsis in resource-poor countries. The data highlight the need for systematic and representative sampling and quality-controlled culture facilities.

## Risk factors for maternal sepsis

Risk factors for puerperal sepsis described in resource-rich countries include: home birth in unhygienic conditions, low socioeconomic status, poor nutrition, primiparity, anaemia, prolonged rupture of membranes (PROM), prolonged labour, multiple vaginal examinations (more than five), caesarean section, instrumental deliveries, retained products of conception, and post-partum haemorrhage.<sup>54</sup> Widely accepted interventions to reduce the incidence of puerperal sepsis are the use of aseptic and sterile techniques (hand cleansing, and sterile drapes and instruments), and antibiotics targeted to deliveries by caesarean section, and those with PROM<sup>55</sup> (which can be associated with *S agalactiae* carriage).<sup>56</sup>

Data on risk factors for puerperal sepsis in sub-Saharan Africa are limited and are likely to differ in relative importance to those in resource rich countries. Whilst high prevalence of HIV/AIDS, anaemia, malaria, and undernutrition is widely reported,<sup>57-59</sup> their contribution to puerperal and maternal sepsis is largely unknown.

HIV/AIDS is, however, a well-recognised risk factor for maternal mortality and morbidity in sub-Saharan Africa. A population based, prospective study of 19 983 women in Rakai, Uganda,<sup>10</sup> reported maternal mortality ratios of 1687 and 310 per 100 000 births in HIV-positive and HIV-negative mothers respectively. This finding is supported by the autopsy study in Mozambique, where HIV/AIDS-related conditions were the most common non-obstetric cause of death (12.9% due to opportunistic infection [bacterial, fungal, and viral]) and the confidential enquiry into maternal deaths in South Africa—HIV/AIDS-related conditions accounted for 20.1% of all maternal deaths.<sup>25</sup> A high burden of morbidity post partum was described in mothers infected with HIV in Kenya.<sup>8</sup> This prospective study

followed up 535 women infected with HIV for a year post partum and reported 33 cases of pneumonia per 100 person years.

Operative or instrumental delivery is likely to be an association. In Nigeria, 14.7% of cases of puerperal sepsis followed caesarean section;<sup>27</sup> however, without knowledge of the prevalence of this mode of delivery and indications for caesarean section, these results are difficult to interpret. In the prospective study on maternal morbidity from west Africa, although five of 18 cases (28%) of puerperal sepsis cases followed caesarean section, this represented a relatively low (1.5%) postoperative infection rate.<sup>30</sup> The authors attribute this result to widespread and systematic antibiotic use in study areas.

Episiotomy is another potential risk factor. The cefoxitin trial in South Africa<sup>31</sup> reported puerperal sepsis in 43 of 195 (22.1%) women with an episiotomy, compared to 33 of 229 (14.4%) without. Other risk factors similar to resource-rich settings were reported from this study, and PROM and increased number of vaginal examinations were significantly associated with puerperal sepsis.<sup>31</sup> Other simple interventions, identified in the community study in Mwanza, Tanzania,<sup>34</sup> significantly reducing the prevalence of puerperal sepsis, were bathing and shaving before delivery.

Genital-tract bacterial carriage might also predispose to (clinically defined) puerperal sepsis. A hospital based study in Zimbabwe reported increased prevalence of *N gonorrhoeae*, *Bacteroides* spp, *Chlamydia* spp, and *Gardnerella vaginalis* among mothers who developed puerperal sepsis,<sup>60</sup> similar to isolates from cases of puerperal sepsis in the Kenyan study described<sup>33</sup> and supported by a separate study in Zimbabwe associating maternal colonisation with *N gonorrhoeae*, *S agalactiae*, and *Bacteroides* spp with PROM.<sup>61</sup>

However, a multicentre study from Zimbabwe (Lusaka), Malawi (Blantyre and Lilongwe), and Tanzania (Dar es Salaam) aiming to reduce chorioamnionitis (on the basis of histological diagnosis) found that although oral antibiotics (metronidazole and erythromycin) at 24-weeks gestation reduced infection with *Trichomonas vaginalis* and bacterial vaginosis, there was no significant reduction in chorioamnionitis at delivery. Oral antibiotics (metronidazole and ampicillin) were also given at birth.<sup>62</sup>

The relative importance of risk factors for maternal sepsis in sub-Saharan Africa depends both on the extent to which they predispose to infection, and their prevalence. More work is needed to establish the relative importance of risk factors in sub-Saharan Africa, since these risk factors might guide more effective antibiotic prophylaxis and offer new strategies for prevention. Research from a resource-poor setting outside of sub-Saharan Africa (Nepal) found a 40% reduction in maternal mortality with vitamin A or  $\beta$ -carotene maternal supplementation, although the extent to which this resulted from decreased maternal deaths from sepsis could not be reliably determined.<sup>63</sup> However, this study does demonstrate that there might be simple prevention methods besides antisepsis and antibiotic measures that could be effective in reducing maternal sepsis and resultant maternal mortality.

## Risk factors for early onset neonatal sepsis

Common risk factors for neonatal sepsis in sub-Saharan Africa have been identified as prematurity,<sup>45, 46, 64</sup> PROM,<sup>41, 45, 64, 65</sup> maternal pyrexia,<sup>51, 64, 65</sup> low birthweight,<sup>46, 52</sup> and difficulties at delivery (obstructed labour or birth asphyxia).<sup>47, 51</sup> These accord with risk factors identified in resource-rich settings, where they are used in a risk-based approach for intrapartum or early antibiotic treatment of neonates to prevent severe disease. However, by contrast with resource-rich countries, mothers with a history of a previous baby with *S agalactiae* infection or urinary tract infections are seldom identified in sub-Saharan Africa, probably because they were not investigated by bacterial culture.

Another approach in resource-rich countries to prevent early onset neonatal bacterial sepsis from *S agalactiae* (using intrapartum antibiotics) is through maternal genital tract screening.<sup>11</sup> Whereas there have been no studies using screening to guide antibiotic prophylaxis in sub-Saharan Africa, several studies have looked at the prevalence of maternal *S agalactiae* genital tract carriage. Because early studies of early onset neonatal bacterial sepsis suggested a low incidence of *S agalactiae* neonatal sepsis, maternal carriage found in Nigeria, Ethiopia, and The Gambia were thought surprisingly high (13–22%).<sup>66,70</sup> Low incidence of neonatal sepsis due to *S agalactiae* were attributed to less-invasive serotypes or neonatal protection from maternal antibodies. However, in view of more recent data on early onset neonatal bacterial sepsis aetiology, the results of these carriage studies are likely to be correct in their suggestion of *S agalactiae* prevalence, but the low actual numbers of mothers colonised and included in the studies would limit their power to detect early onset neonatal bacterial sepsis from *S agalactiae*.

Given the resources required for a screening-based approach to guide intrapartum antibiotic prophylaxis to prevent early onset neonatal bacterial sepsis, an approach based on risk factors is likely to be more applicable in sub-Saharan Africa. Some of the risk factors for early onset neonatal bacterial sepsis in sub-Saharan Africa are probably similar to those described in resource-rich settings, but have not been tested in the context of high rates of HIV, maternal undernutrition, fetal anaemia, and placental malaria. Although these risk factors have been linked to poor neonatal outcomes in sub-Saharan Africa,<sup>71</sup> they have not been studied in relation to early onset neonatal bacterial sepsis in sub-Saharan Africa. This is of particular importance since the identification of additional risk factors for early onset neonatal bacterial sepsis could lead to effective simple prevention measures. Newer potential interventions such as maternal micronutrient supplementation might also contribute to preventing early onset neonatal bacterial sepsis. In a randomised trial of Tanzanian mothers infected with HIV (using multivitamins, vitamin A, or placebo arms to the trial), maternal micronutrient supplementation (but not vitamin A supplementation alone) decreased the risk of neonatal death, low birthweight, severe preterm birth, and small size for gestational age at birth; it also increased maternal CD3, CD4, and CD8 T-cell counts.<sup>72</sup> Whether neonatal effects would be seen in mothers uninfected with HIV is unclear, and it is unknown whether early onset neonatal bacterial sepsis can be prevented. However, the Tanzanian study illustrates the need for epidemiological data and broad thinking in design of future prevention strategies to reduce early onset neonatal bacterial sepsis in sub-Saharan Africa.

## Future strategies

There are many potential opportunities for reducing the burden of early onset neonatal bacterial and maternal sepsis. However, the benefit of any intervention (or package of interventions) can only be maximised if devised using high quality, reliable data on the burden and causes of morbidity. Observational data would ideally come from a large, population-based, multicentre study of maternal genital-tract carriage, with follow-up and microbiological investigation (based on clinical criteria) of neonatal and maternal sepsis and associated risk factors.

Recent consensus has highlighted the need for research priorities focused on health policy and systems research to reduce neonatal sepsis through assessment of the feasibility, effectiveness, and cost of promoting clean delivery practices in homes, primary-care facilities, and referral hospitals.<sup>73</sup> These practices are supported by the experience of resource-rich countries and community-based studies in sub-Saharan Africa, such as the use of the clean delivery kit in Mwanza, Tanzania.<sup>34</sup>

However, there is also the potential for new interventions, which can be broadly divided into two groups: those aimed specifically at reducing infection in the peri-partum period using antiseptics measures and antibiotic prophylaxis (risk-based or from universal screening), and reducing susceptibility to infection by improving maternal health through nutritional supplementation, improved accessibility to antiretroviral therapy, investigation for and treatment of sexually transmitted infections, or, in the future, immunisation. The first approach targets facility-based deliveries, although the second would be mainly community-based and requires increased provision and uptake of antenatal care early in pregnancy.

Interventions should be targeted at the population they serve and the health-care facilities available. In the community, clean delivery practices should be prioritised. In referral centres with high-risk populations, new strategies should be developed, particularly the identification of risk factors for maternal and early onset neonatal bacterial sepsis in sub-Saharan Africa, which could be prevented through antibiotic prophylaxis.

Failure of progress towards MDGs four and five has made addressing these issues more urgent. It is likely that simple, straightforward strategies could prove effective in reducing sepsis. A purely descriptive study with reliable microbiological facilities would provide a sound foundation on which to base future intervention studies. However, a multi-armed, factorial trial with a combination of health interventions could result in the same background information and a more rapid advance in our understanding of the epidemiology and prevention of sepsis. Subsequent analyses would determine risk-groups in which interventions were most effective, ensuring optimum targeting of public-health interventions.

## Conclusions

Despite a considerable burden of disease, there are strikingly few data on the precise incidence and aetiology of maternal or early onset neonatal bacterial sepsis in sub-Saharan Africa, largely because of a lack of reliable microbiological facilities. Simple intervention strategies are effective in other populations and evidence from a small number of intervention studies in sub-Saharan Africa supports the urgent need for further trials, so that public-health measures can be effectively directed and neonatal and maternal morbidity and mortality in sub-Saharan Africa is substantially reduced.

## Search strategy and selection criteria

Data were identified using online searches of PubMed (January, 1966–March, 2009), the Cochrane Library and regional databases (African Index Medicus), accessed through WHO. Search terms included the following in various combinations: “maternal”, “neonatal”, “puerperal”, “sepsis”, “morbidity”, “mortality”, “carriage”, “colonisation”, “Africa”, “sub-Saharan”, “HIV”, “prevention”, and “intervention”. Reference lists of the identified articles were then searched to identify further relevant articles. Articles were selected on the basis of data originating from sub-Saharan Africa (unless in the context of interventions that could be applicable in this region) and their provision of estimates of incidence, aetiology, and risk factors for early onset neonatal bacterial sepsis or maternal sepsis. Data on incidence of early onset neonatal bacterial sepsis were based on papers providing microbiological diagnoses, but due to the paucity of published work on maternal sepsis, published data based on both clinical and microbiological diagnoses were included. No language or date restrictions were placed on these searches.

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Table 1

## Summary of maternal morbidity data

	Location	Study type	Population	Definition of sepsis	Results	Organisms	Limitations
Dare et al <sup>27</sup>	Ife State Hospital, Nigeria	Retrospective review of medical records, referral hospital based	8428 deliveries	Clinical features: pyrexia, lower abdominal pain, subinvolution of the uterus, foul-smelling lochia or vaginal discharge, septic wounds, or bacterial growth from the genital tract	146 (1.7%) mothers with puerperal sepsis	Genital tract cultures: <i>Staphylococcus aureus</i> 29 (19.9%), <i>Klebsiella</i> spp 10 (6.9%), <i>Pseudomonas</i> spp 11 (7.5%), <i>Proteus</i> spp 17 (11.6%), <i>Escherichia coli</i> 18 (12.3%), no growth 55 (37.7%).	Single referral-hospital-based study, retrospective, no anaerobic cultures
Lagro et al <sup>28</sup>	Mpongwe Mission Hospital, Zambia	Prospective, hospital based, opportunistic interviewing, systematic vaginal-swab screening	620 women attending hospital for any reason postpartum	Lower abdominal pain, pyrexia, offensive vaginal discharge up to 3 months postpartum	Symptoms present in 58 of 620 (9%) women	89 of 513 (17%) vaginal swabs abnormal (pus cells, <i>Trichomonas vaginalis</i> , or Gram-negative diplococci on Gram stain)	Single hospital-based study, opportunistic sampling might bias population sample, details of microbiology not reported
Menéndez et al <sup>26</sup>	Maputo, Mozambique	Prospective, referral-hospital-based, study of maternal deaths by autopsy	139 autopsies of 179 maternal deaths	Macroscopic and histological diagnoses defined by autopsy	14 (10.1%) maternal deaths due to puerperal sepsis, 67 (48.2%) due to other infectious diseases; 18 (12.9%) HIV-positive with AIDS-related conditions, 17 (12.2%) pneumonia, 2 (1.4%) tuberculosis, 10 (7.2%) meningitis, 3 (2.2%) severe sepsis	NA	Single referral-hospital-based study might not represent maternal deaths in community
Perine et al <sup>29</sup>	St Paul's Hospital, Addis Ababa, Ethiopia	Prospective hospital study, admissions for puerperal sepsis (and outpatient surveillance of pelvic inflammatory disease)	67 admissions puerperal sepsis (15–28 years)	Pyrexia for more than 48 h after delivery, no extragenital cause, investigated through cultures of samples from the uterus, blood, urine, and pus	45 positive cultures, 22 negative	Enterobacteriaceae 24 (36%), <i>Neisseria gonorrhoeae</i> 19 (28%), <i>Streptococcus</i> spp 16 (25%), anaerobes 3 (4%)	Single-site hospital-based, a third (22) of women were culture negative
Pruat et al <sup>30</sup>	Abidjan (Ivory Coast), Bamako (Mali), Niamey (Niger), Nouakchott (Mauritania), Ouagadougou	Prospective, population-based surveillance study	19 545 pregnant women	Severe sepsis, peritonitis, and odorous vaginal discharge leading to hospitalisation, hysterectomy, or death	18 cases (1.4%) of puerperal sepsis, maternal morbidity ratio 90 (95% CI 50–140) per	NA	Survey: no systematic microbiological investigation

	Location	Study type	Population	Definition of sepsis	Results	Organisms	Limitations
Sebitloane et al <sup>31</sup>	(Burkina Faso), Saint-Louis, Kafrine, Fatick, (Senegal) King Edwards VIII and Addington Hospital, Durban, South Africa	Intervention trial, hospital based: randomisation to intravenous cefoxitin (n=213) or placebo (n=211)	716 enrolled, 675 included: women infected with HIV planning vaginal deliveries	Pyrexia (38°C) and lower abdominal tenderness with offensive or purulent lochia (endometritis), a broken down or infected episiotomy wound with exudates, urinary tract infections, or mastitis or breast abscess	100 000 live births, case fatality ratio 33% Sepsis (19.0% [40 of 211] in placebo group, 16.9% [36 of 213] in cefoxitin group); cefoxitin significantly reduced endometritis (13.6% [26 of 191] in placebo group, 6.4% [12 of 188] in cefoxitin group [p=0.019])	NA	Single hospital-based study, only mothers infected with HIV, no microbiology
Taha et al <sup>32</sup>	Queen Elizabeth Hospital, Blantyre, Malawi	Intervention trial based in referral hospital: chlorhexidine manual wipe of birth canal	6965 hospital births, 241 attended post partum with a problem	Pyrexia over 38°C with offensive vaginal discharge, infected lochia, infected episiotomy or caesarean section wound, retained products of conception, or secondary post-partum haemorrhage	6 of 107 (5.6%) women during intervention vs 17 of 134 (12.7%) during non-intervention period admitted post partum with puerperal sepsis, rates of 1.7 and 5.1 cases per 1000 deliveries (p=0.02)	NA	Single referral-hospital-based study, no microbiology, passive follow up
Temmerman <sup>33</sup>	Nairobi, Kenya	Prospective hospital-based study	35 women with clinical post-partum endometritis (day 7–9) and 30 women without (as controls)	Two or more of: pyrexia, foul lochia, uterine tenderness, or uterine subinvolution; cervical and endometrial sampling	35 women post-partum endometritis, 30 asymptomatic women postpartum controls	12 cases N gonorrhoeae and Chlamydia trachomatis vs 3 controls (p<0.05), isolation Mycoplasma hominis and Ureaplasma urealyticum similar in cases and controls	Single-site hospital-based study, no organism isolated in two-thirds of cases
Winani et al <sup>34</sup>	10 surveillance sites across two rural districts of Mwanza, Tanzania	Intervention trial, community based: mothers given education on clean delivery and clean delivery kit to use	3262 pregnant women (17–45 years)	Pyrexia, abdominal pain or foul lochia, follow up to 6 days	Puerperal sepsis diagnosed 1.1% of users of kit and 3.6% not using (odds ratio 3.2, 95% CI 1.85–5.63)	NA	Not randomised trial, follow up to 6 days only, no microbiology
Wollast et al <sup>35</sup>	Rural villages within areas of Bobo-Dioulasso, Koudougou, and	Prospective community-based study, follow up by newly trained	6129 pregnant women	Persistent pyrexia post partum, follow-up minimum 48 h post delivery	7 (6.2%) women with any post-partum problems had persisting	NA	Only 31% of the expected number of births registered, no microbiology, short

	<b>Location</b>	<b>Study type</b>	<b>Population</b>	<b>Definition of sepsis</b>	<b>Results</b>	<b>Organisms</b>	<b>Limitations</b>
	Zabre, Burkina Faso	traditional birth attendants			fever, 0-1% of all deliveries		follow up

NA=not applicable.

Table 2

## Summary of neonatal morbidity data

	Location	Study type	Population	Definition of sepsis	Results (EOS if available)	Organisms (EOS if available)	Limitations
Gray et al <sup>38</sup>	Queen Elizabeth Hospital, Malawi	Prospective descriptive study, referral hospital, EOS specified	3159 in-born and out-born neonatal hospital admissions, 681 investigated with blood cultures	Culture of <i>Streptococcus agalactiae</i> (blood or CSF); investigation based on clinical suspicion	EOS: <i>S. agalactiae</i> isolated in 29 of 681 cases (blood or CSF), rate 0.92 per 1000 live births	<i>S. agalactiae</i> 29	Single-site referral hospital; rate might be underestimated through lack of presentation to health care facility
Berkley et al <sup>39</sup>	Kilifi District Hospital, Kenya	Prospective surveillance study, district hospital, EOS specified	867 in-born and out-born neonatal hospital admissions under 7 days	Positive blood culture	EOS: 117 positive blood cultures, 5.46 per 1000 live births had neonatal bacteraemia	<i>Escherichia coli</i> 25 (19%), <i>Acinetobacter</i> spp 16 (12%), <i>Klebsiella</i> spp 13 (10%), <i>S. agalactiae</i> 11 (9%), <i>Staphylococcus aureus</i> 7 (5%), <i>Pseudomonas</i> spp 6 (5%), <i>Streptococcus pneumoniae</i> 5 (4%), <i>Streptococcus pyogenes</i> 3 (2%)	Single site; rate might be underestimated through lack of presentation to health care facility
Airedo <sup>40</sup>	Ios University Teaching Hospital, Nigeria	Prospective descriptive study, referral hospital, EOS not specified	In-born (76%) and out-born (24%) neonatal admissions with suspected sepsis	Positive blood culture; investigation based on clinical suspicion	99 positive blood cultures, neonatal sepsis 6.5 per 1000 live births (in-borns)	<i>Klebsiella</i> spp 27 (37%), <i>S. aureus</i> 27 (37%), others ( <i>E. coli</i> , <i>Acetabacterium faecalis</i> , <i>Citrobacter difficile</i> )	Single site, in-born neonates only for rate, EOS not specified
Nathoo et al <sup>41</sup>	Harare Hospital, Zimbabwe	Prospective descriptive study, referral hospital, EOS (defined as less than 48 h) specified	In-born (89%) and out-born (11%) neonatal admissions: 161 hospital admissions with positive blood cultures	Positive blood cultures	Neonatal sepsis 21 per 1000 live births (in-borns)	EOS less than 48 h: 110 positive cultures: <i>S. aureus</i> 34 (31%), non-lactose fermenting coliforms 15 (14%), <i>S. agalactiae</i> 13 (12%), other <i>Streptococcus</i> spp 13 (12%), <i>Staphylococcus epidermidis</i> 10 (9%), <i>Klebsiella</i> spp 9 (8%), lactose-fermenting coliforms 6 (5%), <i>E. coli</i> 5 (5%), others 5 (5%)	Single-site referral centre, investigation of blood based on clinical suspicion, high-risk maternal deliveries
Mulholland et al <sup>42</sup>	Fajara and Royal Victoria Hospital, Banjul, The Gambia	Prospective descriptive study, outpatient department and referral hospital, EOS not specified	Out-born neonatal admissions, 497 enrolled and 239 investigated	Positive blood cultures or CSF in young infants (younger than 91 days), investigation on the basis of clinical suspicion	53 cases of young infant sepsis, 4.42 per 1000 live births (extrapolated from given data)	38 positive blood cultures (without meningitis): <i>S. aureus</i> (17), <i>S. pneumoniae</i> (3), <i>Salmonella</i> spp (5), <i>E. coli</i> (3), other enterobacteriaceae (4), <i>S. pyogenes</i> (3), <i>S. agalactiae</i> (1), <i>Moraxella</i> spp (1), group G streptococci (1)	EOS numbers low in study based on out-patients or referrals
Taha et al <sup>32</sup>	Queen Elizabeth Hospital, Malawi	Intervention trial based in referral hospital: chlorhexidine	6965 women giving birth in hospital	Clinical diagnosis on: temperature higher than	Neonatal sepsis admissions 7.8 per 1000 live births with intervention vs 17.9	NA	Single-site referral centre, no microbiology

	Location	Study type	Population	Definition of sepsis	Results (EOS if available)	Organisms (EOS if available)	Limitations
Sebitloane et al <sup>31</sup>	King Edwards VIII and Addington Hospital, Durban, South Africa	Intervention trial, hospital based: randomisation to intravenous cefoxitin (n=213) or placebo (n=211)	716 enrolled, 675 included: HIV infected women planning vaginal deliveries	38°C, poor feeding, and apnoea or irregular respiration	per 1000 without (p<0.0002), EOS admissions 2.8% (16 of 571) with and 6.4% (36 of 563) without	NA	Single site, only mothers positive for HIV, no microbiology
Wimani et al <sup>34</sup>	Mwanza, Tanzania	Intervention trial community based: mothers given education on clean delivery and clean delivery kit to use	3262 pregnant women (17–45 years)	Clinical diagnosis of cord infection	Cord infection in five (0.3%) infants of kit-users and 48 infants of non kit-users (3.9%) (p<0.001)	NA	Not randomised, use of kit dependent on motivation of mothers enrolled, no microbiology
Muhe et al <sup>43</sup>	Ethio-Swedish Children's Hospital, Addis Ababa, Ethiopia	Prospective descriptive study, referral hospital, EOS not specified	405 infant admissions (under 3 months)	Positive blood (or CSF culture), investigation based on clinical suspicion	41 isolates (blood) from 40 infants, 15 isolates from CSF	<i>S pneumoniae</i> 10, <i>S pyogenes</i> 9, <i>Salmonella</i> spp 5, positive CSF cultures predominantly <i>S pneumoniae</i> 7	Recruitment on the basis of out-patient referrals, likely to miss severe early onset infections (rapidly fatal)
Milledge et al <sup>44</sup>	Queen Elizabeth Hospital, Blantyre, Malawi	Prospective descriptive study, referral hospital, EOS specified	In-born neonates (94%)	Positive blood or CSF culture; investigation on the basis of clinical suspicion	EOS: 380 (48%) isolates	<i>EOS: S agalactiae</i> 61 (16%), <i>S aureus</i> 57 (15%), <i>E coli</i> 41 (11%), <i>Klebsiella</i> spp 41 (11%)	Single-site referral hospital
Laving et al <sup>45</sup>	Kenyatta National Hospital, Nairobi, Kenya	Prospective descriptive study, referral hospital, EOS not specified	In-born neonates	Positive CSF culture, investigation based on clinical suspicion	84 patients investigated, 15 positive cultures	<i>E coli</i> 7 (47%), <i>S agalactiae</i> 4 (27%), <i>Klebsiella pneumoniae</i> 2 (13%)	Single-site referral hospital
Madhi et al <sup>46</sup>	Chris Hani Baragwanath Hospital, Soweto, South Africa	Retrospective review of culture-positive cases <i>S agalactiae</i> , provincial hospital, EOS specified	Paediatric admissions	Positive blood or CSF culture for <i>S agalactiae</i> , investigation based on clinical suspicion	208 of 220 paediatric admissions with <i>S agalactiae</i> sepsis, 63% EOS	<i>EOS from S agalactiae</i> : 2 - 06 per 1000 births	Single-site referral hospital
English et al <sup>47</sup>	Kilifi District Hospital, Kenya	Prospective study infant admissions, district hospital, EOS specified	In-born and out-born neonates	Positive blood or CSF culture	EOS: 41 of 432 positive cultures	<i>EOS: Klebsiella spp</i> (10), <i>E coli</i> (8), <i>S agalactiae</i> (6)	Single site, small numbers for EOS (41 positive isolates)
Udo et al <sup>48</sup>	University of Calabar Teaching Hospital, Nigeria	Retrospective review of infant admissions, EOS not specified	In-born and outborn neonatal admissions	Positive blood culture, investigation	178 positive blood cultures	<i>S aureus</i> 109 (61.2%), unclassified <i>coliforms</i> 39 (21.9%), <i>Streptococcus spp</i> 15	Single site, retrospective study

	Location	Study type	Population	Definition of sepsis	Results (EOS if available)	Organisms (EOS if available)	Limitations
Ghiorgnis <sup>49</sup>	Ethio-Swedish Children's Hospital, Addis Ababa, Ethiopia	Retrospective review of neonatal sepsis admissions, referral hospital, EOS not specified	In-born and outborn neonatal admissions (542)	based on clinical suspicion Positive blood culture, investigation based on clinical suspicion	Neonatal sepsis rate 11 per 1000 live births (in-borns), 151 of 542 positive cultures	(8.5%), <i>enterobacteriaceae</i> 5 (2.8%) <i>Klebsiella</i> spp 34 (38%), <i>E coli</i> 9 (11%), <i>Pseudomonas</i> spp 5 (7%), <i>S epidermidis</i> 13 (25%)	Single site, retrospective review of admissions
Adejuyigbe et al <sup>50</sup>	Outpatient department, Ile-Ife, Nigeria	Prospective descriptive study bacterial isolates from young infants, EOS not specified	Infants attending outpatients (7–55 days old)	Positive blood culture, investigation on the basis of clinical suspicion	54 of 124 positive blood cultures	<i>S aureus</i> 28, <i>Staphylococcus</i> spp 17, <i>Proteus vulgaris</i> 3	Single site, out-born infants only, no EOS
Ojukwu et al <sup>51</sup>	Ebonyi State University Teaching Hospital, Abakaliki, Nigeria	Prospective descriptive study, referral hospital, EOS specified	In-born and outborn neonatal admissions	Positive blood culture; investigation based on clinical suspicion	Neonatal sepsis rate 7.98 per 1000 live births (in-borns), 33 of 138 positive blood cultures (19 of 92 in-born and 14 of 46 out-born), 20 from EOS	<i>EOS: S aureus</i> 7 (35%), <i>E coli</i> 4 (20%), <i>Streptococcus</i> spp 3 (15%), <i>Klebsiella</i> spp 2 (10%)	Single-site referral centre

.. =no data. CSF=cerebrospinal fluid. EOS=early onset neonatal bacterial sepsis. NA=not applicable.