Published in final edited form as:
Lancet. 2010 April 24; 375(9724): 1482–1490. doi:10.1016/S0140-6736(09)61712-8.

INFECTION – RELATED STILLBIRTHS

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Abstract

Infection is an important cause of stillbirth world-wide; in low and middle income countries (LMICs), 50% or more are likely caused by infection. In contrast, in high income countries, only10-25% of stillbirths are caused by infection. Syphilis, where prevalent, causes the majority of infectious stillbirths and is the infection most amenable to screening and treatment. Ascending bacterial infection is a common cause of stillbirth, but prevention has proven elusive. Many viral infections are causal for stillbirth but aside from vaccination for common childhood diseases, it is unclear how most viral-caused stillbirths may be prevented. Malaria, because of its high prevalence and extensive placental damage accounts for large numbers of stillbirths. Intermittent malarial prophylaxis and insecticide impregnated bed nets should decrease stillbirths. Many animal and vector-borne infections cause stillbirth. Because this relationship is especially important in LMICs, research that more clearly defines this relationship is crucial to reduce the unacceptably high stillbirth rates in those areas.

Keywords

Stillbirth; infection; congenital syphilis; vector-borne infections

Introduction

Stillbirth, defined as a newborn having no sign of life at delivery, is one of the most common adverse outcomes of pregnancy; 3.2 million or more occur worldwide each year with 98% or more occurring in low and middle income countries (LMICs).[1–3] In LMICs, stillbirths rates generally range from 20 to 40 per 1000 births, with rates as high as 100/1000 in some areas, compared to 3 to 5 per 1000 births in most high income countries.[1–3] In many LMICs, infections appear to account for 50% or more of stillbirths, while in high income countries, from 10 to 25% of stillbirths are attributed to maternal or fetal infections.[4–6] In a literature review of stillbirth in LMICs, of the five factors having a stillbirth population attributable fraction (PAF) greater than 50%, two - syphilis and chorioamnionitis - were infection-related.[7] Important non-infectious causes of stillbirth include congenital anomalies, placental insufficiency, placental abruption, and asphyxia.[8,9]

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The lower limits of gestational age and birth weight used to define stillbirth vary across geographic areas and have ranged from 20 to 28 weeks and from 350 to 1000 g, respectively.[3] Infection is more clearly associated with early (<28 weeks) compared with late stillbirth (>28 weeks) and with lower birthweight.[5,6,10] Because of these relationships, studies that evaluate only late fetal deaths will miss the large contribution of infection to stillbirths.

For many reasons, the relationship between infection and stillbirth is often unclear.[5,6] Most importantly, infection is seldom apparent from the case history or physical examination of the mother or fetus. Histologic evaluations of the placenta, placental cultures, and fetal autopsies may miss important infections. In addition, even with evidence of infection, it is often difficult to know precisely why a specific stillbirth occurred. Neither positive serologic tests nor organisms in the placenta or fetus prove causality.[4–7,10] Finally, infection may initiate a chain of events leading to stillbirth, and its contribution to fetal death may not be appreciated (e.g., rubella infections causing congenital anomalies). Which stillbirths are attributed to infection depends in part upon the extent of the evaluation and the classification system used.[11]

In LMICs, placental histologic examination, culture, and fetal autopsies are usually unavailable. In high income countries, these generally are available but are not routinely performed. Thus, because confirming an infectious etiology of stillbirth, at a minimum, requires use of these techniques, we believe that the contribution of infections as causal for stillbirth is significantly under-diagnosed in both types of settings. Furthermore, it is likely that if routine bacterial and viral cultures were supplanted by more sophisticated molecular techniques, the apparent contribution of infection to stillbirth would rise still further. An example of this phenomenon, the Coxsackie virus as a cause of unexplained stillbirths, is discussed later in this paper.[12]

Mechanisms

Infection may cause stillbirth by a variety of mechanisms. A maternal infection may lead to systemic illness with the mother becoming severely ill, e.g. severe influenza. Because of high maternal fever, respiratory distress, or other systemic reactions, the fetus may die without organisms transmitted to the placenta or fetus.[13,14] The placenta may be directly infected, resulting in reduced blood flow to the fetus, as seen in malaria.[15] The fetus may be directly infected with damage to a vital organ.[16] If an infection occurs early in gestation, the fetus may not die immediately but may develop a congenital anomaly with fetal death occurring later due to the anomaly.[17] Finally, a maternal infection of the genital tract or elsewhere may precipitate preterm labor that the fetus is unable to tolerate.[18] Thus, there are a number of mechanisms by which infection may result in stillbirth.

The search strategy for this review is described in Panel 1. We identified at least 40 organisms/infections with sufficient evidence to be implicated as a cause of fetal death.[6] These include many different bacteria, viruses, parasites and fungi. While we will not review each organism, we have highlighted those that are important numerically or have evidence suggesting that further research might be valuable.

Bacterial infections

More than 130 different bacteria may be involved in intrauterine infections; many of these[4,6] have also been associated with stillbirth. The types of organisms and the mechanisms by which they cause fetal death are similar across geographic areas. However, the proportion of pregnancies affected by bacterial infection is much higher in LMICs.[3,7] Bacterial infections leading to stillbirth may be divided into 1) those that reach the fetal compartment through

the placenta, and 2) infections that ascend from the vagina through the cervix. In transplacental infections, the placental villi often show evidence of infection and since the organisms enter the fetus through the umbilical vein, the liver is the organ most often infected. Syphilis is an excellent example of a transplacental infection.

Syphilis

Of all the potential infectious causes of stillbirth worldwide, syphilis stands out because it causes a large number of stillbirths but is eminently preventable. *Treponema pallidum* is the spirochete responsible for syphilis. The rate of infection among women of reproductive age varies from as high as 20% among some African populations to about 0.02% in high income countries.[19–23] Spirochetes can cross the placenta and infect the fetus, with risk of fetal infection related to maternal syphilis stage. If the mother is infected but untreated, about 40% of fetuses will die *in utero* and another 30% to 40% will be born alive but have congenital syphilis. More than one million cases of congenital syphilis occur world-wide each year.[24,25] The most common cause of fetal death appears to be placental infection with decreasing blood flow to the fetus, although direct fetal infection also plays a role.[26] Most studies report syphilis to have a relative risk of stillbirth in the range of 2 to 5; however, a Tanzanian study reported a relative risk of 18 for women with active syphilis.[27] In some areas of sub-Saharan Africa, between 25% and 50% of all stillbirths are associated with syphilis.[22] Syphilis also contributes to stillbirths in other areas of the world including Russia, Asia and South America.[28–30]

Stillbirths due to syphilis should be easy to eradicate. Within a functioning health system, it is feasible to screen pregnant women for syphilis and once diagnosed, easy and inexpensive to treat. Women who have been treated for syphilis have a similar or slightly greater stillbirth risk compared to non-infected women.[31,32] The reasons for the current failure to eliminate congenital syphilis – especially in sub-Saharan Africa – include: 1) many women do not have access to or utilize prenatal care, and because of 2) lack of resources, 3) a poorly functioning supply system, and 4) other priorities such as HIV screening and treatment, appropriate syphilis-related care is often not provided. To address some of these issues, a recent study suggested that point-of-care rapid testing and treatment is the most cost-effective method to reduce adverse pregnancy outcomes associated with syphilis.[33] Schmid et al converted the fetal/neonatal consequences of maternal syphilis into disability-adjusted life years (DALYs). They suggested that when stillbirth is included, the cost of one DALY saved was about $10 (US) and was 25 times less expensive than the cost of preventing one DALY among infants born to HIV-positive women.[24,25] Based on these and other data, the World Health Organization has launched a program to eliminate congenital syphilis worldwide.[34]

A number of other spirochetal diseases are associated with stillbirth. Lyme disease, a systemic illness caused by the tick-borne *Borrelia burgdorferi*, was first associated with stillbirth in 1987.[35] Small series of stillbirths associated with maternal Lyme disease have been reported, with most fetal deaths occurring in the mid-trimester. Spirochetes have been found in fetal liver, spleen, kidney, and brain. However, larger-scale serologic studies have shown that few stillbirths are associated with Lyme disease except in highly endemic areas.[36] In Tanzania, more than 30% of adults are seropositive for *B burgdorferi*[37] compared to 2% in the US and Norway, but whether Lyme disease is an important cause of stillbirths in African settings is unknown. Another spirochetal disease associated with adverse pregnancy outcomes, primarily in sub-Saharan Africa, is tick-borne relapsing fever, caused by *Borrelia duttonii*. One study reported a perinatal mortality rate of 30%.[38] In the Democratic Republic of Congo, 6.4% of pregnant women admitted to a maternity ward had

relapsing fever.[39] As with Lyme disease, in most African settings, the prevalence of tick-borne relapsing fever and its contribution to stillbirths is unknown.[40,41]

Listeria monocytogenes is another example of a hematogenously transmitted organism that causes fetal death.[42] The mother acquires this infection by eating contaminated food such as unpasteurized soft cheese or undercooked meat. During bacteremia, the organisms are transmitted to the placenta and may cause villous necrosis and microabscesses. The organisms may be transmitted to the fetus, and stillborns, when they occur, are attributed both to placental dysfunction, and fetal infection. Transplacental infections have also been reported in association with maternal tularemia, clostridia, anthrax, typhoid fever, brucellosis, *Haemophilus influenzae*, *Pseudomonas pyocyanea*, a plant bacterium, *Agrobacterium radiobacter* and tuberculosis (TB).[6] With TB, in addition to the rare transplacental infection causing stillbirth, maternal cachexia associated with late diagnosis and advanced disease also appears to be a risk factor for stillbirth.[43] Although still generally rare in pregnancy, TB rates are increasing in many locations, especially in sub-Saharan African countries where HIV is prevalent. Whether co-infection increases the risk of stillbirth compared to the risk from HIV alone is unclear.[44] In any case, with the exception of syphilis, how often bacterial transplacental infection-related stillbirths occur in LMICs is largely unstudied. However, because of high maternal infectious disease prevalence in LMICs, transplacental infections with a number of bacterial species are likely a common occurrence.

Ascending Bacterial Infections

Organisms that ascend from the vagina into the uterus enter the amniotic fluid either through intact choriodecidual membranes or after membrane rupture.[45] The most common organ infected is the fetal lung, associated with fetal breathing of contaminated amniotic fluid. This mechanism explains why a common autopsy finding in many stillbirths is pneumonitis. Whether the fetus is stillborn with pneumonitis or is born alive with pneumonia depends on factors such as organism virulence, the fetal response, and time between infection and delivery. Romero et al hypothesized that a preterm infection usually elicits a fetal inflammatory response and ultimately preterm labor. However, if the fetus cannot initiate an adequate inflammatory response, the outcome is likely to be a stillbirth.[46,47] Births before 28 weeks appear to be strongly associated with an intrauterine bacterial infection, whereas late preterm births are less likely to have an associated intrauterine infection.[5,10] Therefore, the apparent prevalence of this condition will depend on whether all stillbirths >20 weeks are evaluated or only later gestational age stillbirths are included. In virtually all studies evaluating chorioamnionitis, the frequency of histologic chorioamnionitis in stillbirths is at least several times greater than in controls; whether this implies causation is unknown.[7,48,49] In these studies, the percentage of stillbirths with histologic chorioamnionitis has varied substantially, but approximately half the studies report rates of 70% or more among stillbirths.[46] In a recent study from Australia, Lahra et al[48] found that 37% of all stillbirths were *associated* with histologic chorioamnionitis. They also showed that very early preterm stillbirths as well as postterm stillbirths had substantially higher rates of histologic chorioamnionitis than other stillbirths. (Figure 2) There are also a number of autopsy studies where organisms such as group B Streptococcus, *E coli*, and Klebsiella have been cultured from fetal heart blood, liver, lung, or brain.[50–53] As an example, *E coli* was found in 25% of stillborn heart blood samples in Zimbabwe. Naeye et al[54] studied stillbirths in Ethiopia and compared these results to the US Collaborative Perinatal Study findings. The types of organisms associated with ascending infections were similar in both locations, but the frequency of stillbirth associated with infection was several times greater in Ethiopia. The authors speculated that the difference had to do with greater exposure to infectious organisms, as well as a decreased immune response, secondary to the malnutrition so

prevalent in African populations. Prevention of stillbirths associated with ascending bacterial infection in the presence of intact membranes has proven elusive. To date, no strategies – including antibiotic prophylaxis - appear to prevent the intrauterine infection or the associated stillbirths,[55] although antibiotic treatment targeting bacterial vaginosis may be of value in some women.[56] In women with preterm premature membrane rupture, prophylactic antibiotics reduce histologic chorioamnionitis, but to date have not shown a similar reduction in stilllbirths.[57]

Viral diseases

Although it is clear that viruses cause stillbirths, the overall nature of this relationship is not well-studied, especially in LMICs. Reasons for difficulty in understanding this relationship include the complexity and expense in culturing most viruses, as well as the technical difficulty and expense associated with the polymerase chain reaction (PCR) for viral DNA or RNA identification. Few of these tests are routinely available in high income countries and almost never in LMICs. For this reason, the relative importance of maternal viral infection as a cause of stillbirth in most areas of the world is unknown.

Although the data vary, many studies show a small but often statistically insignificant increase in stillbirth associated with maternal HIV-1 infection.[32,58–59] One meta-analysis, conducted prior to the general use of antiretroviral therapies, suggested a significant 3-fold increase.[60] Among women with HIV-1, risk of stillbirth appears to increase as maternal HIV disease worsens and CD4 counts drop.[58] Since the virus rarely crosses the placenta or infects the fetus until labor, it is not likely that this increase in stillbirths is directly caused by fetal HIV-1 infection. Instead, the stillbirth risk is likely attributed to maternal co-morbidities and overall poor maternal health status, both of which are of particular concern in LMICs. Since the prevalence of maternal HIV-1 may be over 20% in sub-Saharan countries, the contribution of maternal HIV-1 infection to stillbirths in those areas is likely to be important. The concern that combination antiretroviral treatment may contribute to an increase in stillbirth in women with HIV-1 has not been borne out.[61]

Maternal infections with each of the common viral childhood illnesses (rubella, measles, mumps and chickenpox) have been implicated in stillbirths.[62–67] Maternal rubella was associated with congenital cataracts by Gregg in 1941.[65] Subsequently, other anomalies have been documented, including major cardiac defects, some resulting in stillbirth later in pregnancy. Rubella also infects the placenta, enhancing the risk of stillbirth, and can apparently do so without fetal spread.[17] Rubella outbreaks are routinely reported from many LMICs; however, their contribution to stillbirths in LMICs is unknown.[66] Maternal infection with both mumps and rubeola, (measles), have also been implicated as a cause of stillbirth,[64] and both viruses have been isolated from fetal tissues. In Guinea-Bissau, stillbirth rates were increased 4- to 9-fold if the mother was infected with measles during her pregnancy.[67] Varicella (chickenpox) infections during pregnancy may cause maternal pneumonia, placing infected women at risk for death as well as stillbirth. The virus also occasionally crosses the placenta and attacks the fetus directly.[63] These observations confirm that maternal infection with viruses that cause common childhood illnesses increase the risk of stillbirth. Because of widespread immunization in high income countries, maternal infection with these organisms is extremely rare and few stillbirths due to these infections are reported. However, with vaccination rates at 50% or less in many LMICs, stillbirths associated with these infections likely occur. Universal vaccination for childhood diseases should eliminate these stillbirths.

Historically, maternal influenza infection is associated with excess maternal and fetal deaths, but little data is available from LMICs.[68] In the recent epidemic, Severe Acute Respiratory Syndrome was demonstrated to be associated with placental and fetal pathology, although its

association with pregnancy outcome needs further research.[69] There are few reports of H1N1 influenza virus infections in pregnancy, but there is a reported case of a maternal death and stillbirth associated with this infection.[70] The American College of Obstetricians and Gynecologists (ACOG) recommends immunization for all women who will be pregnant during the influenza season.[71] Since influenza infections are common in LMICs, and immunization for these viruses rarely occurs, the potential for an increase in stillbirths associated with various types of influenza infections is strong.

Though not studied in LMICs, in high income countries one of the best described relationships between any virus and stillbirth involves parvovirus B19.[72–76] Parvovirus causes a common childhood rash, erythema infectiosum, as well as aplastic anemia in children with sickle cell disease. Parvovirus can cross the placenta and preferentially attacks erythropoietic tissue, causing severe fetal anemia, non-immune hydrops, and fetal death.[74,75] Parvovirus can also cause stillbirth by directly attacking fetal cardiac tissue resulting in cardiac damage, without associated hydrops. Prior parvovirus infection elicits an antibody response that protects against subsequent maternal and fetal infection. However, even with a new maternal parvovirus infection, the risk of stillbirth is small.[76,77] In the US, it appears that less than 1% of all stillbirths result from parvovirus infection. However, in a report from Sweden, where PCR for viral DNA defined parvovirus infection, 15% of all stillbirths were attributed to parvovirus.[75] In another Swedish study, 8% of stillbirths were due to parvovirus with similar rates also reported from Germany.[76,77]

The enterovirus family includes enterovirus, echovirus, Coxsackie virus, and polio. Each can cross the placenta and cause fetal death, but their overall impact on stillbirths, especially in LMICs, is unknown. In a detailed evaluation of unexplained perinatal deaths, Nuovo et al found Coxsackie virus present in 48% of cases.[12] They emphasized that the histologic findings in the placenta were often non-specific and underscored the need for molecular testing to define this relationship. Furthermore, in a study from Sweden, among 21 women with stillbirth, 52% were Coxsackie virus positive, whereas among controls, only 22% were positive.[78] Echovirus and enteroviruses have also been cultured from stillborns. In most studies, unless the virus was specifically sought at autopsy with sophisticated molecular techniques, an infectious cause of stillbirth would have been missed. Similarly, cytomegalovirus (CMV) has rarely been sought in cases of stillbirth.[79,80] In an Australian study, 9% of blood samples taken from stillbirths by cardiac puncture were PCR-positive for CMV.[81] A recent study from Greece using PCR, showed significantly increased levels of CMV (16%) in the placentas of stillbirths compared to controls (3%).[82] Since CMV is the most common cause of congenital infection, and because of its ability to infect the fetus leading to fetal growth restriction and central nervous system damage, the relationship between CMV and stillbirth warrants further research. Hepatitis and herpes simplex infections have also been described as a cause of fetal death.[83]

Finally, newly described viruses are being associated with stillbirth. For example, the Ljungan virus is a recently described picornavirus of bank voles. It was originally isolated in the Ljungan Valley in Sweden and since has been reported in Denmark and the US. A recent small study of pregnant women found the virus in 40% of stillborns but not in any tissues from normal pregnancies. The overall importance of this infection as a cause of stillbirth in any location is unknown.[84]

Protozoal infections

There are a number of protozoal intrauterine infections that have been described to date. Among these, malaria appears to have the strongest association with stillbirth.

Malaria

Forty percent of births worldwide occur in malaria-endemic areas; 30 million of these pregnancies occur yearly in Africa alone.[85] (Figure 1) Malaria is caused by four types of intracellular parasites (especially *Plasmodium falciparum*) transmitted by several mosquito species.[86] Women infected with *P falciparum*, primiparas, and those previously unexposed to malaria generally have the worst outcomes including maternal death, fetal growth restriction, preterm birth and stillbirth.[85–87] Pregnancy outcome is also directly related to the extent of placental malaria, reported to occur in 13–63% of maternal infections.[15,88] Placental insufficiency results from lymphocyte and macrophage accumulation and thickening of the basement membrane, impeding blood flow through the placenta and restricting transport of oxygen and nutrients to the fetus. Severe maternal anemia associated with malaria may also play a role in stillbirth. Malaria organisms can cross the placenta, causing congenital malaria, but the significance of these infections for stillbirth is not clear. A review of studies, mostly from endemic areas, found that placental malaria was associated with twice (odds ratio of 2.19) the stillbirth risk.[89] An Ethiopian population newly infected with malaria had a 7-fold increased risk.[90] A Tanzanian study showed a PAF of malaria for stillbirth of 32%.[91] Together, these findings suggest that malaria is an important cause of stillbirth. Most malaria studies are from Africa, but results from other endemic areas are similar.[92] Overall, because of the large number of women living in endemic areas, the high percentage of women demonstrating placental malaria, and the 2–fold risk of stillbirth, malaria is likely the most important preventable infectious cause of stillbirth in LMICs. Evidence suggests that intermittent anti-malarial prophylaxis and use of insecticide impregnated bed nets may lower the risk of stillbirth and other adverse outcomes associated with malaria.[93,94]

Toxoplasma gondii is a parasite that normally spends its lifecycle in animals, but may be transmitted to humans. Its human infection, toxoplasmosis, is generally asymptomatic or only causes mild disease, but has been identified in case reports as a cause of stillbirth.[95] Among pregnant women in Nigeria, the prevalence of toxoplasma antibodies is more than 80%, compared to 15% in the US.[96] In Zimbabwe, serologic tests for toxoplasmosis were 4-fold more common in mothers of stillbirths than in controls, and in Jordan, the presence of *T gondii* was significantly higher in those with adverse pregnancy outcomes compared to controls (54% vs. 12%, $p<0.02$).[97] Its importance as a cause of stillbirth in LMICs is unknown. Many other protozoal infections - often common in tropical regions - including trypanosomiasis (African sleeping sickness transmitted by the tsetse fly) and Chagas Disease (caused by *Trypanosoma cruzi* in South and Central America), have been associated with stillbirth,[98,99] but the extent of the relationship is unknown.

Other Types of Infections

There is little research on the relationship between various fungal infections and stillbirth, but case reports of candida infections causing stillbirth exist.[6] In addition, an observational study in Sri Lanka showed significant reductions in stillbirth rates associated with anti-helminthic treatment, implicating worm infestations as a possible cause of stillbirth.[100]

Animal and Vector-borne infections

As we reviewed the infectious causes of stillbirth, it became apparent that many of these infections, whether caused by bacteria, viruses or parasites, were animal or vector-borne. (Table 1) The vector-borne infections include malaria, Lyme disease, various tick borne relapsing fevers, dengue fever, African sleeping sickness, Chagas disease and tuleremia. Maternal infections with a primary animal host include Listeriosis, anthrax, brucellosis,

leptospirosis, toxoplasmosis, Q fever, and lymphocytic choriomeningitis. Other animalassociated organisms causing stillbirth such as the Ljungan virus and Streptococcus porcinus have recently been identified.[84,101] Further study of the relationship between animal and vector-borne infections and stillbirth should be undertaken, especially in LMICs.

Prevention of infection-related stillbirths (Table 2)

Low and Middle Income Countries

In many LMICs, the infectious disease burden during pregnancy is extremely high, and it is likely that the stillbirth rate is also high as a result of these infections.[7,54] Therefore, programs that screen for and treat syphilis should have a major impact on the number of stillbirths. Antibiotic treatment for syphilis-infected women appears to be effective in reducing the stillbirth risk almost to that of non-infected women.[30] Reducing maternal malaria infections in endemic areas should also reduce the stillbirth rate. Anti-malarial strategies have been evaluated specifically for implementation during pregnancy.[92,93] These include malaria prophylaxis - and particularly intermittent therapy, as well as use of bed nets impregnated with insecticides. To date, while these strategies have clearly reduced malaria and outcomes such as severe anemia, most studies have not been powered to show improvements in rarer outcomes such as stillbirth. In LMICs, it is also likely that a reduction in bacterial intrauterine infections, if achievable, will have a substantial impact on stillbirth rates. Potential strategies applicable to LMICs which should be tested include nutritional supplementation with calories and/or vitamin/mineral preparations, and a reduction in genital tract bacterial exposure by use of antibiotics or vaginal chlorhexidine washes, and perhaps effective management of both preterm and term PROM.[56,57,102] Achieving high antiviral vaccination rates (rubella, rubeola, varicella, polio) should reduce the stillbirths associated with these infections.

High Income Countries

Because of the lower incidence of infection-related stillbirths in high income countries, and the variety of organisms involved, reducing this component still further may be difficult. However, continued attention to screening and treatment of sexually transmitted infections, and especially syphilis, should minimize the stillbirths associated with these infections. Maintaining high population vaccination rates for the common childhood diseases will keep stillbirths caused by this mechanism a rarity. Although recommended by ACOG and other organizations, it is estimated that only 25% of US pregnant women receive influenza vaccine during the influenza season. Vaccination may reduce the stillbirths associated with this infection. Greater attention to preventing and treating conditions such as Lyme disease might reduce the few stillbirths associated with this condition. Although stillbirths associated with toxoplasmosis rarely occur, educational attention to efforts such as hand washing may have a small effect. A similar small reduction in stillbirths associated with Listeriosis may be achieved by encouraging pregnant women to avoid soft cheeses and various meat and seafood products. The largest potential area for progress in reducing infection-related stillbirths in high income countries appears to lie in those stillbirths associated with intrauterine bacterial infections prior to membrane rupture. Reducing these infections would not only decrease the number of stillbirths, but preterm births as well. To date, there are no effective strategies to reduce this important group of stillbirths, and research that leads to a reduction in intrauterine infection is crucial. Also, from a research perspective, the development of vaccines for some of the viral causes of stillbirth (parvovirus, Coxsackie A and B, CMV) should eliminate some stillbirths. Development of a vaccine protective against Group B *Streptococcus* should reduce the stillbirths associated with this infection.[103,104] Again, however, because of the rarity of these deaths in high income countries, this approach will likely have a small impact on stillbirth rates.

Conclusions

Overall, it is clear that a high quality evaluation is crucial to determine causality of infection for any particular stillbirth. The best evidence of an infectious etiology for a stillbirth is obtained from a carefully performed autopsy and placental examination with appropriate serologic studies, cultures, and DNA/RNA specimens taken for the organisms discussed in this report. New organisms associated with stillbirth should be sought.[105] However, even if an autopsy is not performed, a histologic study of the placenta, membranes, and umbilical cord, with appropriate bacterial, viral, and protozoan serologic studies, culture, and DNA/RNA isolation techniques, will often provide evidence for an infectious etiology.

One of the most compelling observations related to infection and stillbirths, especially in LMICs, is the many unknowns regarding this relationship. For example, it is unknown if the high sero-prevalences of Lyme disease or toxoplasmosis in African settings are associated with increased risk of stillbirth or whether African tick-borne relapsing fever is an important cause of stillbirth. Also, potential causes of stillbirth by conditions such as worm infestations have rarely been considered.[100] We, therefore, believe that research in a number of LMIC settings, using both traditional and the newest molecular and culture techniques, should be conducted so that the full extent of the relationship between stillbirths and infection can be ascertained. Only with this type of research can we hope to define the reasons for the excessive stillbirth burden in these countries and develop strategies to reduce this burden.[106]

Dr Robert L. Goldenberg was asked by Drs Froen and Islam to create this paper for Lancet. He received no funding from any source to write this paper. He outlined the structure of the paper, participated in the literature review, wrote much of the paper, and incorporated suggested changes by the coauthors as well as completed the final draft. Dr Goldenberg has no known conflicts of interest or patents, funding for equipment or drugs; travel or accommodation payments; expert testimony fees; and any patents or patent applications. He chairs the NICHD Stillbirth Network that is doing an observational study on stillbirth etiology in the US for which he receives expenses and a minimal honorarium when attending meetings, and also is an NICHD grant recipient for its Global Network which is now doing a study on maternity care systems related to stillbirth rates in developing countries. Dr Goldenberg is the corresponding author, has had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Elizabeth McClure has received no funding from any source to participate in the writing of this paper. She helped to outline the structure of the paper, performed the literature review, reviewed and participated in creating each draft of the paper including the final draft. She has no conflicts of interest or patents, funding for equipment or drugs; travel or accommodation payments; expert testimony fees; and any patents or patent applications. She is funded through an NICHD training grant at the Department of Epidemiology, UNC School of Public Health and her work at RTI includes participation in the NICHD Global Network on projects related to stillbirth.

Sarah Saleem has received no funding from any source to participate in the writing of this paper. She helped to outline the structure of the paper, reviewed and participated in creating each draft of the paper including the final draft. She has no conflicts of interest or patents, funding for equipment or drugs; travel or accommodation payments; expert testimony fees; and any patents or patent applications. Her work at Aga Khan University includes participation in the NICHD Global Network on projects related to stillbirth.

Uma Reddy has received no funding from any source to participate in the writing of this paper. She helped to conceptualize the paper, thoroughly discussed the role of infection in the etiology of stillbirth with the first author, participated in writing several drafts of the

paper including the final draft. She has reviewed and approved the final draft. She has no conflicts of interest or patents, funding for equipment or drugs; travel or accommodation payments; expert testimony fees; and any patents or patent applications related to this topic. Her work at the NIH includes supervision of the NICHD Stillbirth Network that is doing an observational study on stillbirth etiology in the US.

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Search Strategy

For this review, we were interested in articles that had information on infection and stillbirth in either low and middle income or high income countries. We searched for all relevant articles in Medline, PubMed, and the Cochrane Review through 2009 using specific search terms including stillbirth, perinatal and fetal death, as well as multiple terms for infection and specific organisms. We reviewed all studies on this topic published in English during this period and reviewed English language abstracts of papers published in other languages. In addition, appropriate references from reviewed papers were obtained. We focused on recent and sentinel studies addressing infections that had the potential to cause a significant number of stillbirths worldwide and, through prevention, treatment programs, and further research, were likely or potentially able to contribute to an important reduction in stillbirths.

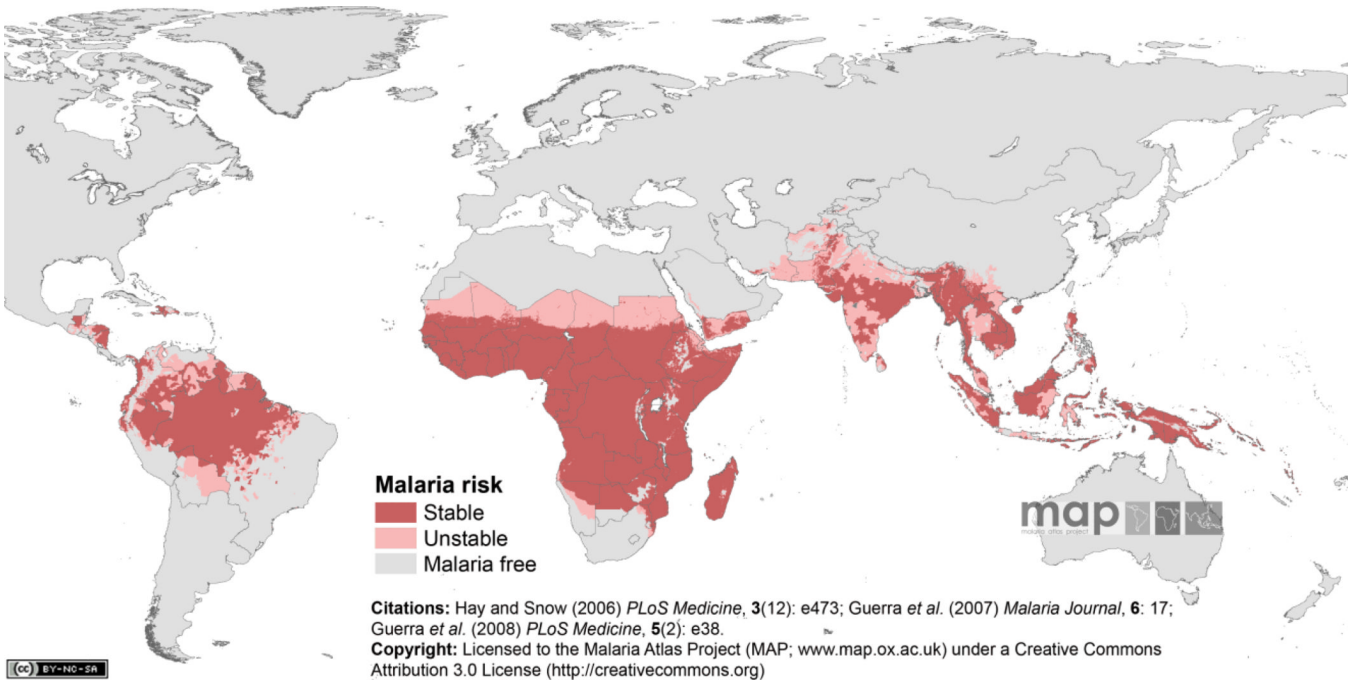

Figure 1. Global Distribution of Malarial Risk (Reference 107)

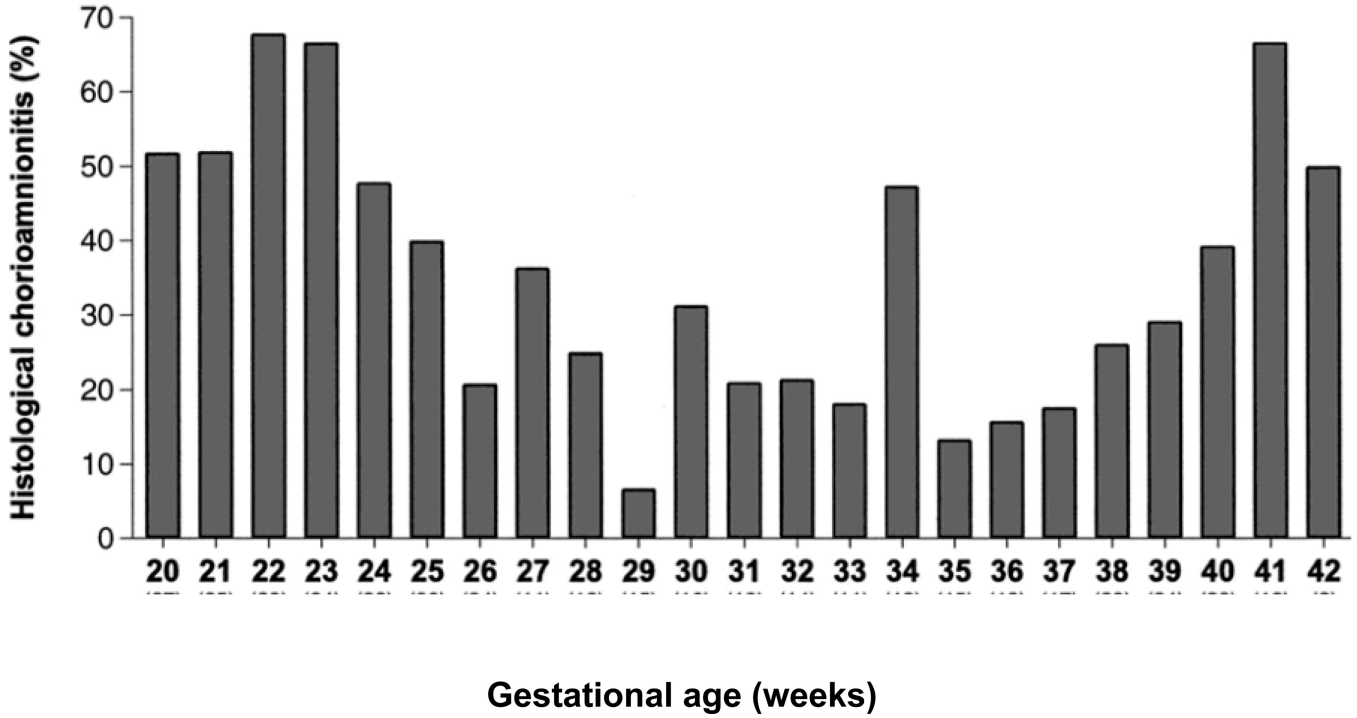

Figure 2. Histologic chorioamnionitis in stillborn babies by gestational age (After Lahra et al, reference 48)

Table 1

Vector-Borne and Animal Derived Maternal Infections Associated with Stillbirth break into vector and animal

Infection	Organism	Vector or Animal Reservoir
Malaria	Plasmodium falciparum	Mosquito
Lyme disease	Borrelia burgdorferi	Tick
Relapsing fever	Borrelia duttonnii	Tick
Tick-borne relapsing fever	Borrelia recurrentis	Tick
African sleeping sickness	Trypanosoma brucei	Tsetse fly
Chagas disease	Trypanosoma cruzi	Triatomine (kissing bug)
Dengue fever	Dengue virus	Mosquito
Tularemia	Francisella tularensis	Tick or deerfly, animal carcasses, contaminated food/water
Listeriosis	Listeria monocytogenes	Domesticated animal products
Anthrax	Bacillus anthracis	Domesticated animals
Q Fever	Coxiella burnetti	Domesticated animals
Brucellosis	Brucella melitenses	Domesticated animals
Leptospirosis	Leptospira interrogans	Dogs, livestock, wild animals
Toxoplasmosis	Toxoplasma gondii	Warm-blooded animals
Lymphocytic choriomeningitis	Lymphocytic choriomeningitis virus	House mouse
Ljungan virus	Ljungan virus	Wild rodents (bank voles)
Streptococcus porcinus	Streptococcus porcinus	Swine

Table 2

Treatment and research priorities to reduce infection-related stillbirth

Treatment Priorities		
Maternal Condition	**Intervention/prevention Strategy**	**Comment**
Syphilis	Syphilis screening and treatment	Intervention is efficacious; effective scale up strategies needed - especially in areas of high prevalence
Malaria	Malaria chemoprophylaxis - directed or intermittentInsecticide treated bed nets	Neither strategy specifically tested when targeted at stillbirth, but these strategies effective against other malarial related pregnancy outcomes
Measles, mumps, rubella, polio, varicella, influenza	Maternal vaccination	Vaccination is effective in preventing maternal disease and likely will prevent stillbirths associated with maternal infection in pregnancy; the contribution of these maternal infections to stillbirth in developing countries is unknown.
Worms	Deworming	Deworming has been shown to be associated with a decrease in stillbirths but a cause and effect relationship is not proven and contribution to burden of stillbirth is unknown.
Research Priorities		
Area of research	**Research direction**	**Comment**
Various maternal infections	Determine burden of infectious causes of stillbirth in developing countries using molecular biological techniques	Proportions of stillbirths in developing countries associated with Lyme disease, relapsing fever, chagas disease, parvovirus, enterovirus, and many other maternal infections are unknown.
Chorioamnionitis	Develop effective prevention and treatment strategies	Since this is likely the most common cause of stillbirth worldwide, research aimed at reducing this infection is crucial.
Viral Infections	Develop vaccines for viral causes of stillbirth including parvovirus, Coxsackie A and B, CMV and test efficacy in preventing stillbirth	Eliminating these infections during pregnancy should reduce stillbirths and other adverse pregnancy outcomes.
Various bacterial infections	Clean delivery practices; maternal vaginal antisepsis (e.g., chlorhexidine); nutrition supplementation, etc	These strategies should be tested to determine their impact on reducing stillbirth.