Should all pregnant women be screened for syphilis?

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In industrialized countries, the incidence of syphilis has decreased dramatically since the discovery of penicillin in the 1940s. However, syphilis and congenital syphilis are far from eradicated, especially in low- and middle-income countries. Syphilis in pregnant women is a cause of adverse pregnancy outcomes that can be prevented by screening for syphilis and early treatment in pregnancy. Several studies have found screening of pregnant women for syphilis to be a highly cost-effective intervention, even if the prevalence of syphilis is low. Obstacles to universal screening of pregnant women include low awareness of syphilis and low quality of antenatal care and healthcare in general in many low- and middle-income countries. For these settings, we need simpler and more reliable serological tests for syphilis, but we also need to strengthen health services in general to ensure sustainable antenatal care services to ensure sustainability of syphilis screening programmes.

The first description of syphilis in nursing infants dates back from the end of the fifteenth century. Initially, wet nurses were thought to be the source of the disease, but in the sixteenth century, the idea gained ground that congenital syphilis may be hereditary. In the nineteenth century, several important observations were made concerning congenital syphilis, but it was not until the development of the first serological test by Wasserman in 1906, that the transmission of syphilis from mother to child could be demonstrated. The concept of screening and treating pregnant women was subsequently developed, and with the discovery of penicillin in 1943, all the tools were available that are needed for the prevention of congenital syphilis. Where are we now, 60 years later?

Syphilis in different parts of the world

In industrialized countries, the incidence of syphilis has decreased dramatically following the introduction of penicillin in the 1940s. Between 1947 and 1956, the reported number of cases of primary and secondary syphilis in the USA, dropped from 66.4/100,000 to 3.9/100,000 [1]. From the late 1950s until 1990, there was an increase in syphilis incidence marked by epidemics that occurred approximately every 10 years. The population subgroups most at risk of syphilis varied from one epidemic to another. The explosive epidemic in 1990 involved men and women, mainly from ethnic minorities, and was thought to be caused by an increase in crack cocaine use associated with an increase in commercial sexual activity. The epidemic took place against a background of increasing poverty and a decline in the provision of health services [1]. Throughout the 1990s, syphilis incidence declined, but from 2000 onwards there has again been an increase in incidence. This latest increase initially mainly involved gay men, but later also the incidence in women increased [2,3]. A similar pattern was seen in Western Europe, with a decrease in syphilis incidence in the early 1990s, followed by an increase that initially mainly involved gay men [4]. The increase in syphilis incidence in Western Europe was independent from the syphilis epidemic that took place in the Russian Federation in the early 1990s. This epidemic coincided with the breakdown of the Soviet Union. Syphilis notification rates were less than 10/100,000 throughout the 1980s up to 1992 and then increased dramatically to over 200/100,000 in 1996 [5].

The decrease in incidence of syphilis combined with screening programmes for pregnant women has resulted in congenital syphilis being a rare occurrence in industrialized countries. In 2005, for example, in the USA, the reported rate of congenital syphilis was 9.1/100,000 live births [3]. However, recent experience from the USA and from Eastern Europe has shown that the incidence of syphilis and of congenital syphilis can increase quite dramatically over a relatively short time period. In the Russian Federation, reported cases of congenital syphilis increased 26-fold between 1991 and 1999, from 29 to 743 [5].

In industrialized countries, surveillance for syphilis is based on notification of cases. In most low- and middle-income countries

Keywords: adverse pregnancy outcome, cost–effectiveness, screening, syphilis

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(LMIC), reporting of diseases is incomplete and disease notification is of little use for surveillance purposes. However, prevalence of reactive syphilis serology in pregnant women can provide a good estimate of the burden of syphilis on women and their offspring. A reactive nontreponemal test (rapid plasma reagin [RPR] or venereal disease research laboratory [VDRL]) in combination with a treponemal test (*Treponema pallidum* hemagglutination assay [TPHA], *Treponema pallidum* particle agglutination assay [TPPA], fluorescent treponemal antibody absorption [FTA-ABS]) is indicative of active or untreated syphilis. Prevalence rates based on a single test (RPR, VDRL or a treponemal test) are overestimates of the prevalence of active syphilis. For example, up to 28% of positive RPR tests in pregnant women may be false positive [6]. In addition, interpretation of syphilis serology may be difficult in areas where nonvenereal treponematoses are still endemic or have only recently been eliminated. However, nonvenereal treponematoses typically occur in foci, in rural areas in underserved populations [7,8].

Table 1 presents a nonexhaustive overview of the prevalence of positive syphilis serology in pregnant women in several LMIC, based on published data of the past 20 years. Most of the prevalence rates reported in the studies from sub-Saharan Africa and Latin America are much higher than prevalence rates that have been reported from industrialised countries. For example, in the UK in the 1990s, prevalence of positive syphilis serology was 0.2% in London and 0.02% elsewhere in the UK [9], whereas most prevalence rates from sub-Saharan Africa and Latin America exceed 1%. Prevalence is especially high in southern and eastern Africa, with rates exceeding 5 and even 10% in some populations. However, data from Botswana do suggest that there has been a decline in syphilis prevalence in the 1990s. In northern Botswana, the prevalence of positive VDRL among pregnant women more than halved between 1992 and 2003, from 12.4 to 4.3%, presumably as a result of changes in sexual behavior [10]. The prevalence rates that were found in Asia are generally lower than what has been found in sub-Saharan Africa and Latin America, with most rates not exceeding 1%.

In conclusion, syphilis continues to be a worldwide public-health problem, with sub-Saharan Africa and Latin America being the worst-affected regions in the world.

Consequences of maternal syphilis: bad news

The first study that quantified the risks of untreated syphilis in pregnant women was conducted in Oslo (Norway) at the end of the nineteenth and beginning of the twentieth century. Boeck found that 26% of babies born from mothers with syphilis were free of infection; 25% were infected but did not have any clinical manifestations; and 49% were diseased [11]. In the first decades of the twentieth century, Harman compared the rates of adverse pregnancy outcome in women who had serological evidence of syphilis during pregnancy and women who did not have syphilis. The rate of miscarriage was 9.2% among the women with syphilis and 7.4% among the women who were free of syphilis. But the differences were especially marked for stillbirths and infant deaths. The respective rates for stillbirth were 8.0 and 2.1%; and for infant death 22.9 and 11.4% [12]. Subsequent studies confirmed the association between untreated syphilis in pregnancy and adverse pregnancy outcome, including miscarriage, prematurity, intrauterine growth retardation, stillbirth, neonatal death and congenital syphilis.

Studies conducted in sub-Saharan Africa in the 1990's, found rates of adverse pregnancy outcome associated with untreated syphilis that were similar to the rates found by Harman [6,13–16]. For example, in the study by Harman, the relative risk of stillbirth associated with positive syphilis serology in pregnancy was 3.8. In sub-Saharan Africa, relative risks have been found ranging from 3.6 to 18.1 [6,13,14], the higher relative risks being associated with higher titres of the RPR, which is suggestive of the early stages of untreated syphilis. Indeed, in the 1950s it was observed that the risk of adverse pregnancy outcome is higher in primary and secondary syphilis than in latent syphilis [17].

The proportion of adverse pregnancy outcomes in a population that can be attributed to syphilis is dependent on the relative risk and on the prevalence of syphilis in the population of pregnant women. In Mwanza (Tanzania), where the prevalence of high titre syphilis was 5.9%, it was estimated that 17% of all adverse pregnancy outcomes, and 51% of stillbirths, among women who had not been screened for syphilis could be attributed to syphilis [18]. In other words, in this population, nearly 1 in 5 cases of adverse pregnancy outcome and 1 in 2 cases of stillbirth would be avoided if syphilis were eliminated.

Table 1. Prevalence of positive syphilis serology among pregnant women.

Country	Year of study	Tests used	Prevalence based on combination of tests (%)	Prevalence based on a single test (%)	Ref.
Africa					
Guinea-Bissau*	1997–1998	RPR & TPHA	3.9		[47]
Burkina Faso	1995–1998	RPR & TPHA	0.24		[48]
Nigeria	1991–1997	VDRL, VDRL & TPHA	0.13 (extrapolated)	1.3	[49]
Ghana	2000–2001	TPHA		7.1	[50]
Cameroon	1994–1996	TPHA		17.4	[51]
Ethiopia	1996–2001	TPHA & RPR	3.2 (1996), 2.2 (2001)		[52]
Ethiopia (rural)	1994	VDRL		13.7	[53]
Kenya (Nairobi)	1992–1997	RPR		6.5 (1992), 3.8 (1997)	[54]
Kenya (Nairobi)	1997–1998	RPR, RPR & TPHA	2.4	3	[55]
Rwanda	1992–1993	RPR		3.8 (HIV–), 6.3 (HIV+)	[56]
Tanzania	1994	TPHA & RPR	8		[57]
Tanzania (country wide)	2003–2004	RPR		7.3	[58]
Zambia	1986–1987	RPR		8	[13]
Zambia	2001–2003	RPR & TPHA/TPPA	4.9 (HIV–), 13.0 (HIV+)		[59]
Malawi	1987–1990	VDRL/RPR & MHA-TP (RPR titer ≥ 1:8)	3.6		[14]
Malawi	2001–2003	RPR & MHA-TP/ TPHA	1.1-1.4 (HIV-), 5.9–7.3 (HIV+)		[59]
South Africa (rural)	1994	RPR		6.5	[60]
South Africa (rural)	1998	RPR		9	[15]
South Africa	1990	RPR & TPHA	14.5		[16]
South Africa	2004–2005 (?)	RPR		2-6.5	[61]
Botswana	1992–2003	VDRL		12.4 (1992), 4.3 (2003)	[10]
Mozambique*	1991	RPR & TPHA	8.8		[62]
Latin-America					
Belize	1993	RPR, RPR & IgG test	2.4	2.8	[63]
Nicaragua	2004	ELISA, RPR & TPHA	1.5		[64]
Cuba	Late 1990s	RPR/ VDRL & FTA-Abs	2.2		[65]
Haiti	1996	RPR & FTA-ABS	6.8		[66]
Bolivia *	1996	RPR & FTA-ABS	4.5		[67]
Argentina	Late 1990s	RPR/ VDRL & FTA-ABS	0.9		[65]
Asia					
Saudi Arabia	Late 1990s	RPR/ VDRL & FTA-ABS	0.1		[65]
India (New Dehli)	Late 1990s	VDRL		0.5	[68]
India (North India)	2002	RPR		5.4	[69]
China	2002	RPR & TPHA	0.2		[70]
Thailand	Late 1990s	RPR/ VDRL & FTA-ABS	0.2		[65]
Thailand	1996	RPR/VDRL & FTA-ABS/TPHA	0.5		[71]
Cambodia	2001	RPR & TPHA	1.3		[101]
South Korea	2000	VDRL & FTA-ABS		0.1	[72]

**Women delivering live infants.ELISA: enzyme-linked immunosorbent assay; FTA-ABS: fluorescent treponemal antibody absorption; HIV–: HIV negative; HIV+: HIV positive; MHA-TP: microhemagglutination assay; RPR: rapid plasma reagin; TPHA: treponema pallidum hemagglutination assay; TPPA: treponema pallidum particle agglutination assay; VDRL: venereal disease research laboratory*

Finally, a recent study from Malawi showed that maternal syphilis increases the risk of mother-to-child transmission of HIV infection. Intrauterine, intrapartum and postpartum transmission of HIV are increased nearly threefold in the presence of syphilis [19]. So, apart from it's effects on congenital syphilis, early screening and treatment of pregnant women may also reduce pediatric HIV infections.

Consequences of maternal syphilis are avoidable

The WHO recommends that syphilis in pregnant women who do not have a penicillin allergy is treated with benzathine penicillin, according to the dosage schedule for nonpregnant women, that is, one dose of 2.4 million IU benzathine penicillin in case of primary, secondary and early latent syphilis, and three doses of benzathine penicillin at weekly intervals in case of late latent syphilis [20]. In a study in the USA this treatment regimen has been shown to be more than 98% efficacious in preventing adverse pregnancy outcome [21]. The few failures that occurred were associated with secondary syphilis and or treatment late in pregnancy.

A prospective study in Mwanza found that one dose of benzathine penicillin was highly efficacious in preventing adverse pregnancy outcome. There was no difference in the risk of adverse pregnancy outcomes between women with syphilis who were treated with one dose of benzathine penicillin, and women who did not have syphilis during pregnancy [18]. However, studies from South Africa, where the Department of Health recommends three doses of benzathine penicillin, suggest that the reduction in adverse pregnancy outcomes is larger in women who receive more than one dose of benzathine penicillin compared with women who receive only a single dose [22]. A possible explanation for the discrepancy between the study from Tanzania and the South African studies, may be that the prevalence of HIV infection was much higher among the women in South Africa than among the women in Tanzania.

While there is no doubt regarding the benefits of treatment of pregnant women with syphilis, at programme level the question is whether it is cost–effective to screen all pregnant women and treat those found to be infected with *Treponema pallidum*. Screening and treatment of syphilis in pregnant women has been found to be highly cost–effective in industrialized countries, even if the prevalence of syphilis in pregnant women is well below 1% [23–25]. In these settings, a programme of screening and treatment is cost–effective because of the low costs of the syphilis tests and treatment of pregnant women, and the high costs of treating congenital syphilis.

There are also several studies from sub-Saharan Africa that found screening and treatment of syphilis to be highly cost–effective [13,26,27]. These studies were from settings where the prevalence of positive syphilis serology in pregnant women was 6.5–8%. However, the cost per disability-adjusted life years (DALY) saved increases and the benefit cost ratio decreases as the prevalence of syphilis and the yield of screening programmes decreases. Terris-Prestholt *et al.* estimated that the cost per DALY saved is approximately US$4 at a prevalence of positive RPR of 15% and US$33 at a prevalence of 2%, that is, when the effects of treatment on stillbirth are included in the computations. These estimates remained well below the upper bound of US$193 per DALY saved, which the World Bank considers as the limit of cost–effectiveness for interventions.

Very few studies have been conducted on the cost–effectiveness of antenatal screening for syphilis in other parts of the world. One study from Thailand found repeat testing for syphilis in the third trimester to be cost–effective at a prevalence, at first antenatal clinic visit, of 2.1% and an incidence of syphilis of 0.07% [28].

The benefit:cost ratio of a syphilis screening programme is dependent on the prevalence of syphilis among pregnant women but also on the proportion of the women with syphilis that receives adequate treatment. In many low-resource settings, pregnant women attend antenatal clinic late in pregnancy and may not return to receive their test results and be treated if needed. In Nairobi, Kenya, testing for syphilis at antenatal clinic ('on-site testing'), instead of shipping the blood samples to a central laboratory, has resulted in a dramatic increase in the proportion of RPR-reactive pregnant women who received treatment from 9.1 to 87.3% [26,29]. Similarly, in South Africa, on-site testing for syphilis resulted in higher percentages of pregnant women being diagnosed and treated compared with off site testing [30].

However, on-site testing has its problems. The test that is mostly used is the RPR, which is very cheap and is considered to be easy to perform. However, this test can not be done on whole blood, and requires cold storage. In addition, the test may give false positive results, up to 28% in pregnant women [6]. In South Africa, use of a

rapid treponemal test, an immunochromatographic strip (ICS), has been found to be more cost–effective for on site screening than the RPR, despite the fact that the ICS is approximately 20-times more expensive than the RPR [31]. Apart from its cost, the test also has the disadvantage that it cannot distinguish between active syphilis and past infection. There is clearly a need for better tests that do not require electricity and are more sensitive and specific. The Sexually Transmitted Diseases Diagnostics Initiative (SDI) of United Nations Children's Fund (UNICEF)/ United Nations Development Programme (UNDP)/ World Bank/WHO has initiated a programme for the development of tests for the diagnosis of sexually transmitted infections (STIs) in low-resource settings [32].

Should all pregnant women be screened for syphilis?

The probability of an adverse pregnancy outcome is more than 50% for a pregnant woman with untreated syphilis. This risk can be reduced substantially with one to three injections of benzathine penicillin, a cheap antibiotic that is affordable to any health service. All pregnant women should have access to this highly efficacious intervention, and this means that all pregnant women should be screened for syphilis. The question is: is this affordable? Cost–effectiveness studies have shown that a programme of screening and treating pregnant women is good value for money. In industrialized countries, screening pregnant women for syphilis remains cost–effective, even as congenital syphilis has become very rare. Moreover, experiences from the Russian Federation and from the USA have shown that syphilis epidemics can be explosive and lead to a sudden increase in maternal syphilis [5,33]. Studies from Africa, where resources for health are scarce, also found syphilis screening and treatment of pregnant women to be highly cost-effective. In addition, newer syphilis tests are being developed, and they hold the promise that screening will become more cost–effective, because they make reliable on-site testing in primary–healthcare settings possible [31,32].

However, policy decisions are not only based on cost–effectiveness analyses. Treatment of HIV-infected adults in sub-Saharan Africa was shown to be less cost–effective than prevention [34,35]. Yet the international community and donor agencies decided to give their full support to antiretroviral treatment (ART) programmes in sub-Saharan Africa and other low-resource countries [36]. A lot of resources and efforts now go into the treatment of HIV-infected adults in developing countries and in the prevention of HIV transmission from mothers to their babies. By comparison, the resources needed for the prevention of congenital syphilis are minimal and there is no reason why more funds cannot be freed to screen and treat all pregnant women for syphilis.

Unfortunately, we are still far away from the goal of achieving universal screening of pregnant women. Gloyd *et al.* examined the policy and data on syphilis screening of 22 countries in sub-Saharan Africa. Uptake of antenatal care was high, with 73% of pregnant women attending antenatal clinic at least once. However, of the women attending antenatal clinic, a mere 38% were tested for syphilis [37]. In Bolivia, only 17% of pregnant women were tested for syphilis [38]. A study from the Russian Federation found that only 55% of pregnant women with active syphilis had received 'some treatment for syphilis' and 41% had received penicillin [38]. Among Medicaid-enrolled women in Florida who attended antenatal clinic, the proportion screened for syphilis doubled between 1995 and 2000 but remain well below the target of universal screening in 2000, that is, 57% [39]. Suboptimal treatment, that is, failure to re-test pregnant women in the third trimester of pregnancy and testing late in pregnancy, have been found to be associated with the occurrence of congenital syphilis in several states in the USA [40,41].

There are several reasons why a high coverage of antenatal screening and treatment of syphilis is still not achieved. In industrialized countries, we have been lulled into believing that syphilis is a problem of the past. The main reason why all pregnant women are not tested for syphilis is the lack of awareness; costs and technical difficulties are not an issue.

In LMIC, lack of awareness may also be a problem, especially in areas where the prevalence of syphilis is not high. But the main bottlenecks are lack of resources for health and the weakness of health services in general. The situation is particularly dramatic, in sub-Saharan Africa, owing to the worsening economic situation and structural readjustment programmes that imposed cuts in public spending, leading to a reduction in resources for healthcare. Staff are demotivated and overburdened, the supply of drugs and other commodities is erratic and infrastructure is poor. International organizations and donor agencies lost interest in health services in developing countries and instead put their money in programmes

to tackle health problems with interventions that are considered to be cost-effective. The HIV/AIDS epidemic, with its impact on development and health services, made matters worse. Fighting HIV/AIDS became a top priority and large funds became available for it. Early in the HIV/AIDS epidemic, other STIs got their share of the attention and funding, as it became clear that control of other STIs is a cost-effective strategy to prevent HIV transmission. However, over the past 5–10 years, attention has shifted to the treatment of HIV-infected persons, with antiretroviral drugs and prevention of mother-to-child transmission of HIV, and control of other STIs has moved down the agenda. Compared with HIV infection in pregnant women and their offspring, syphilis has little visibility. An HIV-infected child is a chronically ill child and is visible for healthcare workers, whereas a stillbirth or a premature delivery can be attributed to several causes other than syphilis. It can be argued that this is one reason why syphilis does not receive the priority attention it deserves. For example, in Ivory Coast and in the Democratic Republic of Congo, prevention of mother-to-child transmission (PMTCT) programmes are well funded and pregnant women are offered free HIV tests, whereas they have to pay for a syphilis test [42,43].

Future perspective

The WHO is putting congenital syphilis back on the agenda [44]. However a major bottleneck to universal screening of syphilis is the under funding of health services in LMIC and the fragmented approach to health problems, which is to a large extent driven by international organizations and donor agencies. Interventions to address a particular health problem may be well funded one year and 'fall out of grace' the next year, and how sure can we be that syphilis will not be out of fashion a few years from now? The idea is gaining ground that we should foster linkages between HIV/AIDS interventions and other reproductive health programmes, including antenatal care, family planning and treatment of other STIs [45]. I would advocate to go even further and to reinstate the concept of primary healthcare that 'starts with people' and their health problems, in this case pregnant women and the risks they run of adverse pregnancy outcome [46].

Acknowledgements

The authors have no relevant financial interests including employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties related to this manuscript.

Executive summary

Syphilis: a worldwide public-health problem

- More than 50 years after the discovery of penicillin, syphilis continues to be a worldwide public-health problem.
- In Africa, Latin America and the Caribbean, the prevalence of syphilis in pregnant women ranges from 0.2% to over 10%.

Maternal syphilis & adverse pregnancy outcome

- Adverse pregnancy outcomes associated with syphilis include miscarriage, prematurity, intrauterine growth retardation, stillbirth, neonatal death and congenital syphilis.
- The probability that a pregnant woman with syphilis has an adverse pregnancy outcome is more than 50%.

Screening & treatment of syphilis in pregnancy

- The risk of adverse pregnancy outcome can be reduced substantially by treating syphilis in pregnant women with one or three doses of benzathin penicillin.
- Several studies have found that screening of pregnant women is a very cost-effective intervention, even if the prevalence of syphilis is low.

All pregnant women should be screened for syphilis

- Studies have shown that programmes of syphilis screening of pregnant women are cost–effective.
- Newer syphilis tests are being developed and they hold the promise that screening will become even more cost–effective.
- Prevention of congenital syphilis is much simpler and cheaper than prevention of HIV transmission from mothers to their babies, for which large resources are freed.

- Linkages have to be fostered between HIV/AIDS programmes and other reproductive health programmes to ensure a sustainable, holistic approach to the reproductive health problems of men, women and pregnant women.

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