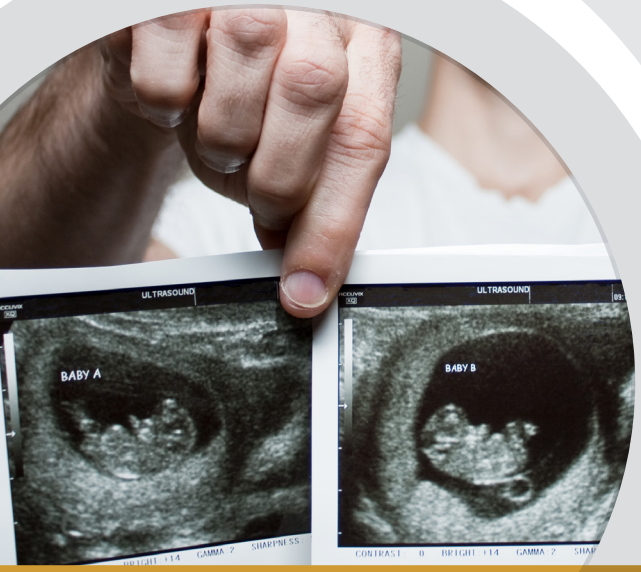


TECHNICAL REPORT

Effectiveness and cost-effectiveness of antenatal screening for HIV, hepatitis B, syphilis and rubella susceptibility

Literature review

www.ecdc.europa.eu

ECDC TECHNICAL REPORT

Effectiveness and cost-effectiveness of antenatal screening for HIV, hepatitis B, syphilis and rubella susceptibility

Literature review

This report was commissioned by the European Centre for Disease Prevention and Control (ECDC) and coordinated by Otilia Mårdh, Tarik Derrough and Andrew Amato-Gauci.

The report was produced under contract ECDC/2012/052 with the National Institute for Health and Welfare (THL) by Carita Savolainen-Kopra, Mia Kontio, Marjukka Mäkelä, Kirsi Liitsola, Jukka Lindeman, Jaana Isojärvi, Heljä-Marja Surcel, Irja Davidkin, Henrikki Brummer-Korvenkontio, Eija Hiltunen-Back, Hanna Nohynek, Tuija Leino, Markku Kuusi, and Mika Salminen.

Helena de Carvalho Gomes and Ana-Belen Escriva are acknowledged for internal ECDC support.

Suggested citation: European Centre for Disease Prevention and Control. Effectiveness and cost-effectiveness of antenatal screening for HIV, hepatitis B, syphilis and rubella susceptibility. Stockholm: ECDC; 2017.

Stockholm, March 2017

ISBN 978-92-9498-035-9
doi: 10.2900/51864
Catalogue number TQ-04-17-185-EN-N

Contents

Figures

Tables

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ANS	Antenatal screening
CBA	Cost benefit analysis
CEA	Cost effectiveness analysis
CRS	Congenital rubella syndrome
CUA	Cost utility analysis
DALY	Disability-adjusted life year
HBeAg	Hepatitis B envelope antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
ICER	Incremental cost-effectiveness ratio
LYG	Life years gained
LYS	Life years saved
MTCT	Mother-to-child transmission
NNS	Number needed to screen
PICO (T)	Patient, intervention, comparative, outcome, time
QALY	Quality-adjusted life year

Glossary

Antenatal screening	Testing of a pregnant woman to detect conditions that may threaten the health of the foetus or child.
Antenatal screening programme	National or regional programme for diagnostic testing of pregnant women to detect certain conditions; programmes clearly state their aims and objectives, include data collection, evaluate results and regularly audit the entire programme.
Effectiveness of antenatal screening	The ability of antenatal screening to reduce or prevent infections during pregnancy that could potentially lead to mother-to-child transmission. In the case of rubella, susceptible mothers are identified.
Effectiveness of antenatal screening as prevention	As above, but extended to the factors influencing the implementation of measures to prevent the infection of the child by vertical (i.e. mother-to-child) transmission at any stage of pregnancy or during infancy and/or breastfeeding.
Operational effectiveness	Provides information on how well the intended programmatic measures (e.g. screening and interventions) are implemented in terms of coverage, specificity, quality and necessary follow-up with regard to the targeted population.
Infant	A child of less than 12 months of age.
Migrant	In this document, the term 'migrant' is used in its widest sense to embrace a number of population groups mentioned in the literature.
Mother-to-child transmission	Transmission of an infectious agent from the mother to the child before birth, during labour and delivery, or during infancy (the first year of life). Also referred to as vertical transmission.
Mandatory screening	Systematic testing at the population level, without the real possibility of declining the test, or a test that is taken as a condition to gain access to care, benefits, services, or any form of application of individual rights (i.e. travel, schooling, day care, employment, etc.). Declining the screening test may lead to sanctions or restrictions of individual civil rights.
Newborn	A child less than one month of age.
Neonatal	Of, relating to, or affecting the newborn and the infant during the first month after birth.
Diagnostic testing	A test in order to identify a health condition of the individual, administered with the explicit intention of clinically managing the condition.
Opt-in testing	Individuals seeking care are informed that testing is recommended. The individual is required to give explicit consent before the test is performed.
Opt-out testing	Testing is performed as part of routine care. Pre-test information is made available, and consent is assumed unless the individual explicitly declines testing.
Rubella susceptibility	Lack of protective antibodies for rubella virus. Protective antibodies can result from natural infection or vaccination.
Universal screening	Testing systematically offered to the entire relevant population (mandatory or voluntary); covers opt-in and opt-out testing.
Prenatal	Before birth; during or relating to pregnancy (synonym for antenatal).
Recommendation	Suggestion or proposal by an authoritative body.

Screening	The systematic application of tests, examinations, or other procedures (in the context of this report, testing for HIV, hepatitis B, syphilis infection or susceptibility for rubella infection), with the intention of identifying previously unrecognised health conditions at the population level. The relevant population is dependent on the condition to be identified and the intended interventions and must be defined.
Selective screening	Testing systematically offered to the entire relevant population (mandatory or voluntary), covers both opt-in and opt-out testing.
Universal screening	The entire relevant population are systematically offered testing (mandatory or voluntary), covers both opt-in and opt-out testing.
Voluntary screening	Testing systematically offered to the entire relevant population whereby refusal does not lead to immediate negative consequences, restrictions of civil rights or sanctions for the individual belonging to that population.
Vulnerable populations	For the purpose of this guidance, subpopulation groups that are at increased risk of contracting HIV, HBV, syphilis or rubella during pregnancy or are already infected, and are hard to reach through antenatal screening programmes.

Executive summary

Background

This literature review of the effectiveness and cost-effectiveness of antenatal screening was conducted as part of a project evaluating the effectiveness of antenatal screening (ANS) for HIV, hepatitis B, syphilis and rubella susceptibility in EU/EEA Member States. The purpose of this review was to provide evidence for guidance to strengthen antenatal screening programmes in Europe.

Methods

The effectiveness of antenatal screening was defined as those factors that influence the population completeness with regard to the detection of infections during pregnancy and factors that could potentially lead to mother-to-child transmission (MTCT). In the case of rubella, this refers to the identification of susceptible mothers.

The cost-effectiveness of ANS was not defined because defining the cost-effectiveness of a preventive intervention is in many ways a value judgement, as the acceptable cost per prevented outcome/gained life year (adjusted or unadjusted) depends on a comparative valuation of different diseases and the economic situation of the country funding the intervention.

The research question was formulated to include the following elements (based on a PICO (T) elements):

- P (population): pregnant women and their unborn children
- I (intervention): national programmes for universal screening
- C (comparator): no screening or screening for high risk groups only
- O (outcome): avoided infections in children and cost per infection avoided
- T (time factor): from maternal screening to confirmation of the child's infection status.

Database searches were performed between 13 October 2011 and 12 March 2014 and covered all EU/EEA countries, the USA, Canada, Australia and New Zealand; search languages were English, Danish, Finnish, German, Norwegian and Swedish.

The literature was screened by two independent researchers; studies were selected based on the agreed inclusion criteria. The study quality was assessed in accordance with the criteria described by Guyatt et al. [1] (effectiveness) and by Drummond et al. [2] (economic evaluations).

Results

This literature review on the effectiveness of antenatal screening for HIV, hepatitis B, syphilis and rubella susceptibility retrieved nine studies on cost-effectiveness and 37 studies on effectiveness that were included in the analysis.

The effectiveness of antenatal screening depends on the coverage of the screening programme, the quality of testing, and the effectiveness of treatment. The ability to reach all pregnant women, the sensitivity of the screening test (i.e. the capacity to identify all infected women), and the preventive treatment received by all infected pregnant women were factors to ensure optimal effectiveness.

The following national antenatal screening programmes were considered cost-effective in comparison with no screening or screening only targeted risk groups: syphilis in Norway and the United Kingdom; HIV in the Netherlands, Australia and New Zealand; hepatitis B in the United Kingdom and Belgium; rubella susceptibility in the Netherlands, especially if targeted at non-vaccinated pregnant women.

This review also showed that only a small number of cost-effectiveness studies has been conducted in Europe.

Conclusions

For HIV, hepatitis B and syphilis, most studies suggest that comprehensive, population-based antenatal screening is cost effective in all assessed settings.

The effectiveness of antenatal screening programmes has not been widely studied in Europe. The available literature mainly provides authors' opinions regarding factors that influence effectiveness; there are no comparative studies on effectiveness. Implementing antenatal screening programmes was found to be cost-effective in several countries.

1 Background

In 2011, ECDC initiated a project to evaluate the effectiveness of antenatal screening programmes for HIV, hepatitis B, syphilis and rubella susceptibility in the EU/EEA.

The project included: 1) a survey of the EU/EEA Member States to obtain information on the current practices of antenatal screening for infectious diseases in order to describe country-specific approaches and identify areas in need for improvement and models of good practice [3]; 2) a literature review of the published literature on effectiveness and cost-effectiveness of antenatal screening.

The aim of the systematic literature reviews was to collect published evidence on the effectiveness and cost-effectiveness of antenatal screening practices for the prevention of mother-to-child transmission (MTCT) of HIV, hepatitis B, syphilis and rubella in the EU/EEA countries in order to inform ECDC guidance on antenatal screening in the EU/EEA.

2 Review methods

2.1 Search strategy

Information specialists conducted a systematic literature search on the cost-effectiveness and effectiveness of screening programmes for the targeted infections during pregnancy (Appendices 1 and 2). The search strategies were developed by experienced information specialists in collaboration with content experts on the basis of the research question (PICO: population, intervention, comparison and outcome/s) to retrieve relevant studies.
A combination of medical headings and keywords was used to search titles and abstracts. The results were combined to exclude duplicates. All reviews were developed by senior information specialists and content experts.

2.1.1 Cost-effectiveness

Research question: Are national programmes for universal antenatal screening for HIV, hepatitis B, syphilis and rubella susceptibility cost-effective?

The following PICO (T) elements were identified for a cost-effectiveness review:

- P (population): pregnant women and their unborn children
- I (intervention): national universal screening programmes for all pregnant women for syphilis, HIV, hepatitis B and rubella susceptibility; therapeutic intervention for those with positive test results (rubella susceptibility, vaccination to prevent MTCT in future pregnancies)
- C (comparator, reference intervention): no screening or screening for high-risk groups only
- O (outcome): avoided infections in children and cost per infection avoided
- T (time factor): from maternal screening sample to confirmation of the child's infection status.

After a discussion with experts, it was decided that life years gained (LYG), life years saved (LYS), and incremental cost-effectiveness ratios (ICER) were also outcomes of interest. As outcome terms were not used in the searches, this additions would not have had any effect on the search.

The references of all included articles were checked for relevant new articles (ancestry search). In October 2011, a comprehensive search on the economic evaluation of screening programmes for syphilis, HIV, and hepatitis B was carried out in the following databases, starting with the publication year 1990: Ovid MEDLINE, Ovid MEDLINE Daily Update, Ovid MEDLINE In-Process & Other Non-Indexed Citations, NLM PubMed (epubs ahead of print), the Centre for Reviews and Dissemination, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials.

Information concerning cost-effectiveness was derived from a systematic literature review on economic evaluations of antenatal screening for syphilis, HIV, and hepatitis B commissioned by the Finnish Institute for Health and Welfare [4] in October 2011 (updated in October 2012). A review of economic evaluations of rubella susceptibility screening was carried out using a similar strategy in October 2012. Both searches were updated in January 2014. The search strategies and results are presented in Appendix 1. Grey literature from was not included.

2.1.2 Effectiveness

Research question: Are national programmes for universal antenatal screening for HIV, hepatitis B, syphilis and rubella susceptibility effective, and what are the factors influencing effectiveness?

The search strategy was based on a cost-effectiveness search, but the term 'cost' or its synonyms were not used as search terms. The time period searched ranged from 2000 to the present; the selected databases were the

same as for the cost-effectiveness search described above. The HIV search was limited to EU/EEA countries, the USA, Canada, Australia, and New Zealand. A second search on ANS effectiveness was conducted on March 2014 in Ovid MEDLINE to ensure that no important studies were missed (the previous search was limited to publications reporting on the cost of screening programmes). The search strategies and results are presented in Appendix 2. Grey literature was not included.

The literature review on cost-effectiveness was based was on the following PICO (T) elements:

- P (population): pregnant women and their unborn children;
- I (intervention): national universal screening programmes for all pregnant women for syphilis, HIV, hepatitis B and for rubella susceptibility; therapeutic intervention for those with positive test results (rubella susceptibility, vaccination to prevent MTCT in future pregnancies)
- C (comparison): no screening or screening for high risk groups only
- O (outcome): avoided infections in children

2.2 Study selection criteria and procedure

The searches were targeted to cost-effectiveness and effectiveness of screening, with the aim of finding relevant evaluations of antenatal screening programmes. Articles describing solely sensitivity and specificity of different tests used for screening were not included because these usually do not provide enough information about test performance in real-world settings. We used data from high-quality screening program evaluations, as assessed using the criteria by Drummond et al. [2] for cost-effectiveness studies and by Guyatt et al. [1] for effectiveness studies.

The exclusion criteria for the cost-effectiveness search were:

- No cost information
- Incorrect infection
- No intervention (e.g. prevalence study)
- Intervention not in line with current practice
- Description or comparison of laboratory methods or diagnostics only
- Language not English, Danish, Finnish, German, Norwegian or Swedish

Other reasons for exclusion were: wrong study design, health service utilisation, treatment, ethical or legal issues, socio-demographic issues, attitudes, prognosis, and education.

The exclusion criteria for the effectiveness search were:

- Publication type without original data (editorial, letter, etc.)
- Country not EU, USA, Canada, Australia or New Zealand
- Not national data (regional, only one city, etc.)
- Population not pregnant women
- No intervention (e.g. prevalence study)
- Intervention not in line with current practice
- Description or comparison of laboratory methods or diagnostics only
- Language not English, Danish, Finnish, German, Norwegian or Swedish
- Other (e.g. treatment, case description)

2.2.1 Cost-effectiveness

Two researchers independently evaluated the titles and abstracts of the retrieved articles and selected potentially relevant articles based on agreed exclusion criteria. Differing choices were discussed and doubtful cases were included.

In the second round, the same researchers evaluated the full-text versions of potentially relevant publications using more detailed inclusion criteria. The given costs had to include screening costs as well as counselling and treatment costs; in addition, the articles had to mention the infections in children. Disease-specific selection criteria were clarified in discussion with infection experts: for syphilis, testing and treatment should be completed in early pregnancy, and in the case of HIV, highly active antiretroviral therapy should be initiated no later than at 28 weeks of gestation. The final selection of included publications was made by consensus. In order to find more cost–benefit analyses, the references/bibliographies of all selected articles were searched for materials published before the search date.

Two researchers independently assessed study quality with the Drummond checklist (economic evaluation) [2]; disagreements were resolved by a third researcher.

2.2.2 Effectiveness

The evaluation procedure for publications on effectiveness was identical to the one on publications on cost-effectiveness: two researchers screened all titles and abstracts and evaluated study quality in accordance with the criteria described by Guyatt et al. [1]. When it became evident that no controlled studies were available, only descriptive results were selected.

3 Review results

3.1 Results of search findings

3.1.1 Cost-effectiveness

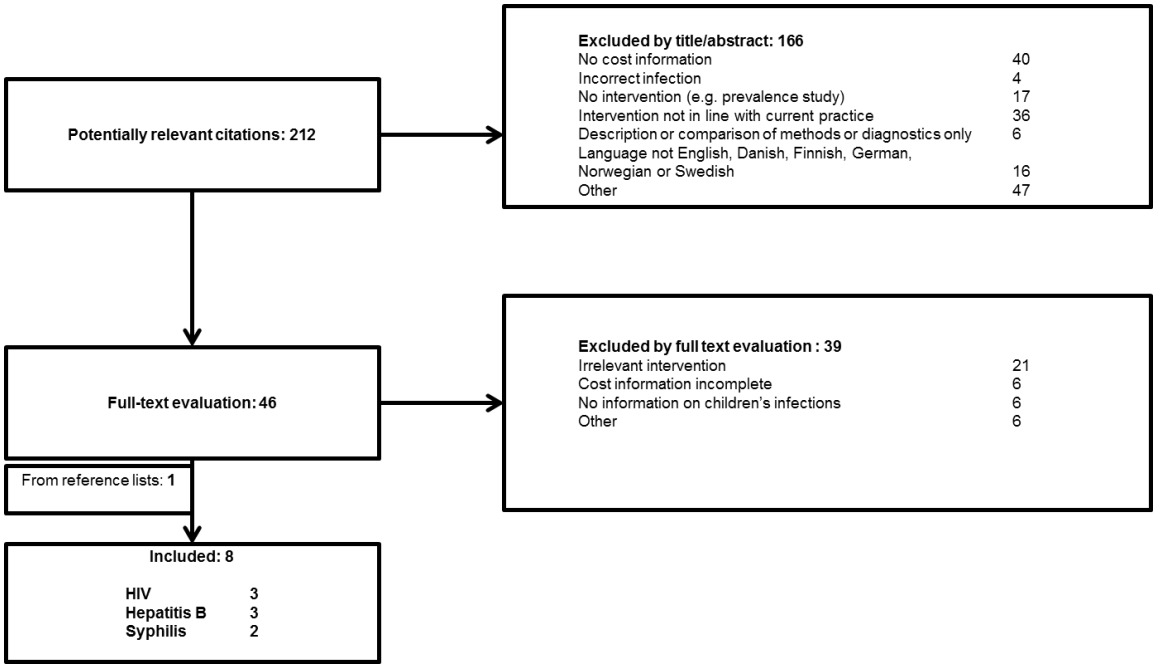
A systematic literature search on the topic of economic evaluation of screening programmes of syphilis, HIV, and hepatitis B in October 2011 identified 212 references. In October 2012, the search was updated but no new articles meeting the inclusion criteria were found.

A search on the topic of economic evaluation of rubella susceptibility screening programmes in October 2012 identified 136 references.

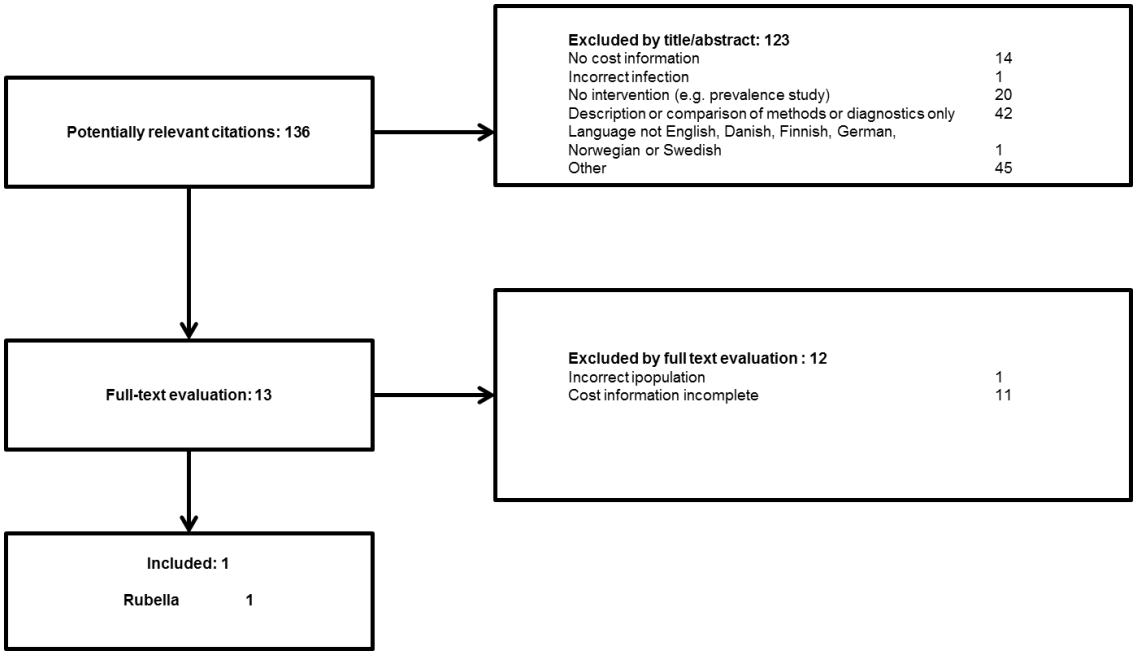
In January 2014, an update of the literature search on the topic of economic evaluations of screening programmes, identified 28 new articles, none of which met the inclusion criteria.

Figure 1. Literature search on the topic of economic evaluation of screening for a) HIV, hepatitis B, syphilis, and b) rubella susceptibility (including reasons for exclusion)

a) Search on the topic of cost-effectiveness of screening programmes for HIV, hepatitis B and syphilis



b) Search on the topic of cost-effectiveness of screening programmes for rubella susceptibility



3.1.2 Effectiveness

A literature search on the topic of effectiveness of antenatal screening for HIV, hepatitis B, syphilis and rubella susceptibility in March 2014 retrieved 261 titles for HIV, 140 for hepatitis B, 160 for syphilis, and 72 for rubella susceptibility. A total of 19 studies for HIV, six for HBV, five for syphilis and seven for rubella susceptibility met the inclusion criteria.

Figure 2. Literature search on the topic of effectiveness of antenatal screening for HIV, supplemented with citations found through ancestry search and citation analysis

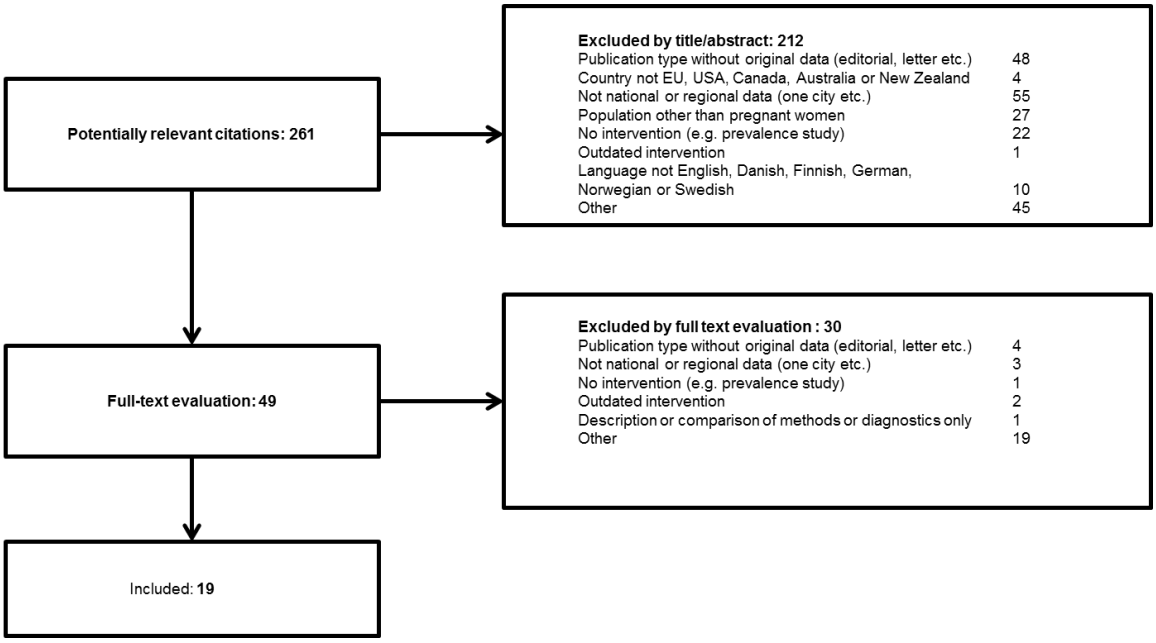


Figure 3. Literature search on the topic of effectiveness of antenatal screening for hepatitis B, supplemented with citations found through ancestry search and citation analysis

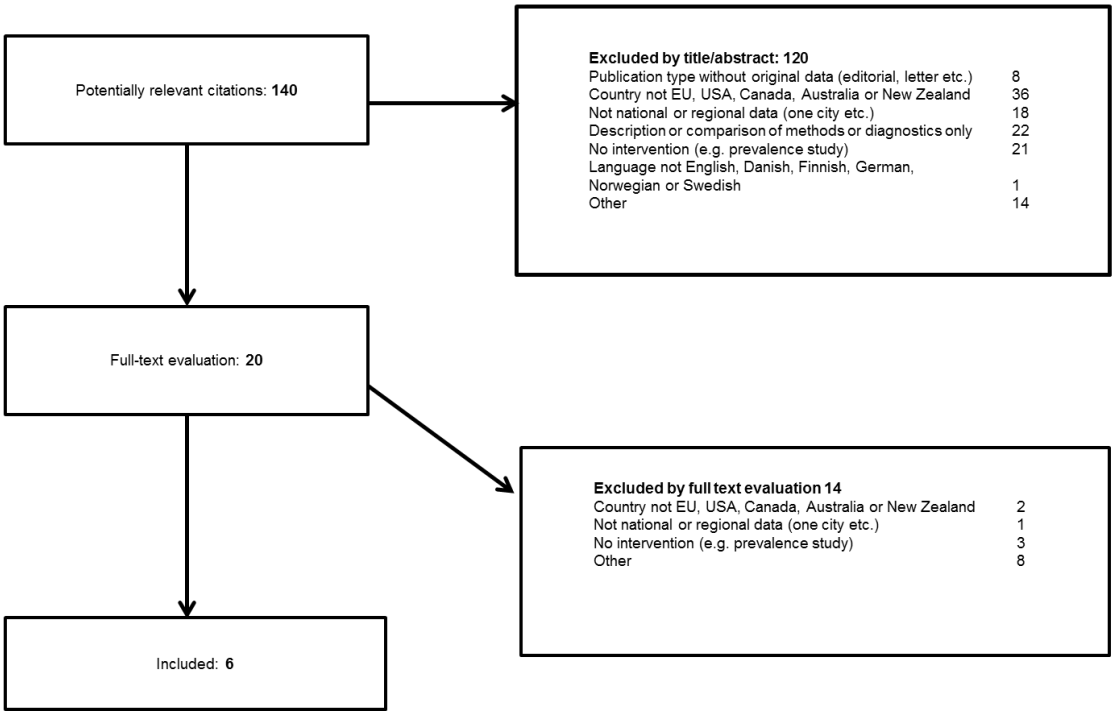


Figure 4. Literature search on the topic of effectiveness of antenatal screening for syphilis, supplemented with citations found through ancestry search and citation analysis

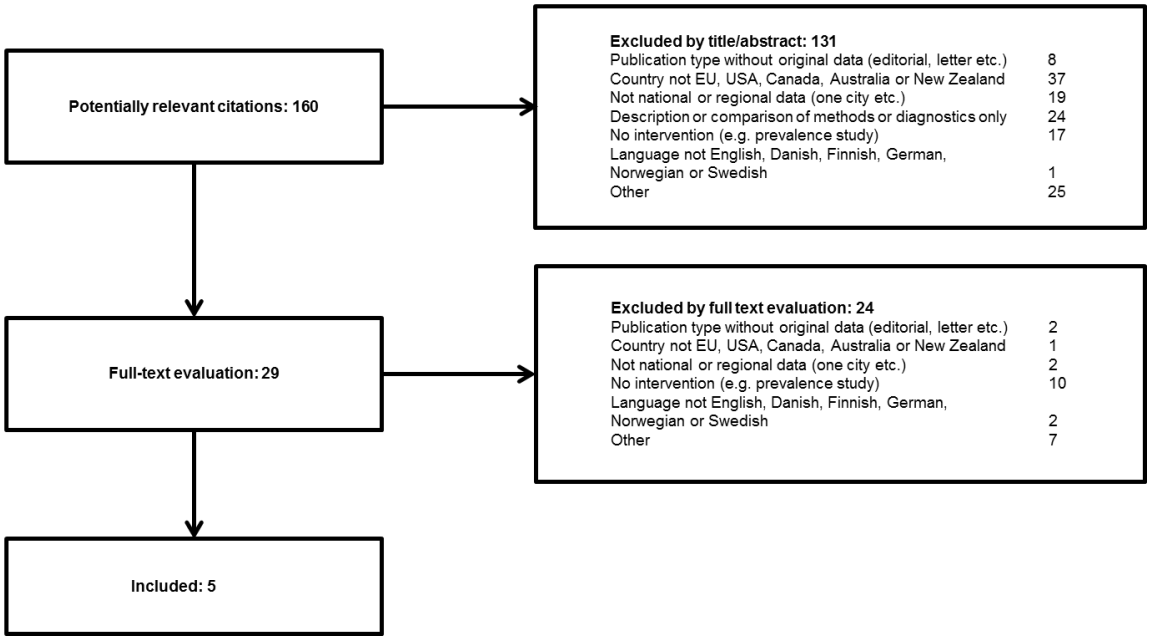
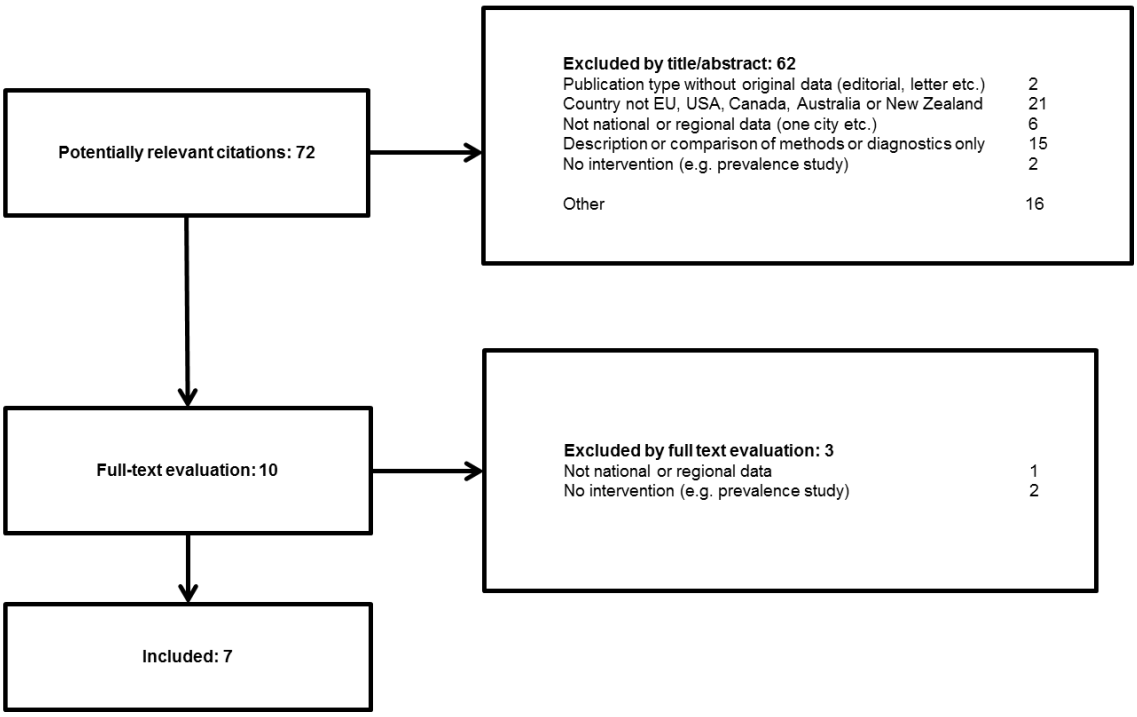


Figure 5. Literature search on the topic of effectiveness of antenatal screening for rubella susceptibility, supplemented with citations found through ancestry search and citation analysis



3.2. HIV

3.2.1 Effectiveness of national programmes for antenatal screening of HIV

The search did not identify any comparative studies on the effectiveness of antenatal screening for HIV.

Eight non-comparative studies [5-12] analysed the effectiveness of antenatal HIV screening. The studies showed that awareness of the HIV infection status is crucial for the prevention of MTCT; reported MTCT cases were mainly associated with the mother's undiagnosed HIV infection. The studies emphasised the importance of antenatal screening for the prevention of MTCT because a high proportion of pregnant women was only recognised as HIV infected after prenatal testing. In some regions, the number of neonatal HIV infections did not decrease in women at high HIV risk who had tested HIV negative during early pregnancy (HIV tests were part of the routine check-up), which warranted repeated testing during late pregnancy. Inclusion in antenatal care and provision of prevention therapies was mentioned as important for pregnant women who tested positive.

In Sweden, a population-based analysis of data on all known mother–child pairs with perinatal exposure to HIV-1 1982–2003 was conducted. A national screening programme offering HIV testing to all women regardless of risk factors or ethnic origin has been in place since 1987 and achieved a high acceptance rate. Screening combined with MTCT prevention measures (i.e. antiretroviral treatment and elective caesarean delivery) has resulted in a significant decrease in the number of infected children; the MTCT rate decreased from 24.7% in 1985–1993 to 5.7% in 1994–1998 and 0.6% in 1999–2003. No child was infected when the mother received two or more antiretroviral drugs [5].

A retrospective study of all HIV-infected women and their children (born in Denmark between January 2000 and May 2005) showed that 21% of the women did not know their HIV status at the beginning of the pregnancy. Eight children were born with HIV. They were all born to mothers whose HIV infection was undiagnosed during pregnancy or delivery [6].

In the Netherlands, the effectiveness of antenatal HIV screening was evaluated by comparing the results from a database on antenatal screening with the data from pregnant women and newborns from other data sources. 40% of the HIV-infected women were only diagnosed during pregnancy. In 2004, the Netherlands introduced universal HIV screening with opt-out. Prior to the introduction of the screening scheme, 5–10 children with HIV were born

every year, a number that dropped to one child per year on average after the introduction of HIV screening. There were no known cases of MTCT when women received antiretroviral therapy [7].

In Alberta, Canada, a retrospective analysis was performed on HIV-infected pregnant women who delivered between January 1999 and February 2006; 43% of HIV-infected pregnant women were unaware of their HIV status prior to prenatal screening. Only one of the 111 infants born to HIV-positive mothers was HIV infected; the mother did not seek prenatal care [8].

In the USA, a significant reduction of perinatal HIV infections was achieved by routine HIV screening of pregnant women and by MTCT prevention measures; in 1991, an estimated 1 650 perinatal infections was reported; in 2002, the numbers were down to between 144 and 236. In 2001, the US Centers for Disease Control and Prevention recommended a routine second HIV test during the third trimester for women with an elevated risk for HIV infection because some regions showed an increasing proportion of MTCT in women who had tested HIV negative earlier in pregnancy [9].

In New York State, the outcome of an MTCT prevention scheme (1988–2008) was assessed based on surveillance, laboratory and programme monitoring data. In 1997, only half of the women received prenatal testing. Since 2002, at least 95% of pregnant women have been tested. The rate of MTCT declined significantly in the same period of time: 11.5% in 1997 versus 1.3% in 2008. MTCT was more likely in the infants of mothers diagnosed with HIV at or after delivery than in those whose mothers were diagnosed earlier and in infants whose mothers did not receive any prenatal care [10]. US data on HIV-exposed singleton deliveries in 1996–2000 were used to study missed opportunities for perinatal HIV prevention. Two major missed opportunities were observed: lack of prenatal care and lack of prenatal HIV diagnosis despite prenatal care [11].

In a study in North Carolina conducted between November 2002 and April 2005, HIV RNA testing was used for all women who were antibody negative at the time of routine testing in order to determine the prevalence of acute (antibody-negative) HIV infection in pregnant women. A total of 0.2% of women tested positive, 3.4% of them had acute HIV infections. One-third of the women with acute HIV infection were pregnant. During the study period, six HIV-infected infants were reported; three were born to women who were antibody negative between 12 and 18 weeks of gestation [12].

Eight studies [13-23] compared the performance of several antenatal HIV screening strategies/policies in relation to achieved coverage of screening programmes. Generally, a universal testing approach with opt-out strategy was considered to be the most effective. However, some regions achieved high testing rates among pregnant women by using an opt-in strategy.

In Denmark, the effectiveness of selective HIV screening for the prevention of MTCT was studied. In 1997, it was recommended that women in high-risk groups should be offered HIV testing during pregnancy. In 2000–2001, three infants born to mothers in high-risk groups were vertically infected – none of the mothers were offered an HIV test during pregnancy. It was concluded that selective screening for HIV during pregnancy was ineffective and should be replaced by a universal offer of HIV testing [19].

A Dutch study compared two antenatal HIV screening strategies: non-selective opt-out and selective opt-in. HIV-infected pregnant women were retrospectively identified from the Dutch HIV cohort 2000–2008 data; HIV-positive infants were identified through a questionnaire distributed to paediatric HIV centres. In 2004, the selective opt-in antenatal HIV screening strategy was replaced by a non-selective opt-out strategy. Opt-out screening in combination with prevention interventions appeared to detect more HIV infections in pregnant women and reduced MTCT substantially: before 2004, only 33% of all HIV-infected pregnant women were diagnosed, while after January 2004, 80% were diagnosed. No HIV-infected children were born to the HIV-infected women whose infection was known before pregnancy or after the first-trimester screening [13].

A study conducted in the UK analysed the effectiveness of universal antenatal screening to reach the HIV-infected pregnant women. Universal antenatal screening was introduced in England in 1999. In Scotland, some regions had a policy of universal testing before 2003, and in mid-2003, the remaining regions implemented testing. The data demonstrated that the universal offering has improved detection rates both in England and Scotland. In England, an estimated 12% of women remained undiagnosed at delivery in 2003 compared with 26% in 2000. In Scotland, 11% of women remained undiagnosed at delivery in 2004 compared with 32% in 2000. The Scottish data revealed that an increasing proportion of women were having their infection diagnosed antenatally [17].

In Catalonia, Spain, where a policy of universal offer of HIV testing for pregnant women has been implemented since 1996, medical records showed an HIV testing uptake rate of 88.3% in 2000 (94% in public and 71% in private hospitals). Study data show that prenatal HIV testing was frequently not documented in medical records and that 10% of women were unaware that they had been tested; for 7.2% of the women who reported HIV testing, this information was not found in the medical records. The main reason for not having had an HIV test was not having been offered the test (65%) [20].

A study conducted in the USA and Canada compared three different prenatal HIV-antibody testing approaches: opt-in, opt-out voluntary testing of pregnant women, and mandatory newborn testing (the newborns are tested for

HIV with or without mother's consent if the mother's HIV status is unknown at delivery). Testing rates among women who gave birth varied depending on the approach: opt-out voluntary testing and mandatory testing of newborns were associated with the highest testing rates. In regions using an opt-in approach, testing rates varied between 25% and 81%, while regions using an opt-out policy reported rates between 71% and 98%. Shifting from an opt-in approach to either opt-out or mandatory newborn testing increased prenatal HIV-testing rates [14]. In California, a 1996 law mandates prenatal care providers to offer HIV tests to all pregnant woman. Data from population-based surveillance of 496 HIV-infected women and their infants, collected between 1987 and 2002, were analysed to compare the change in HIV test offers before and after 1996. Unsurprisingly, there was a significant increase in HIV test offers for the period 1996–2002: between 1987 and 1995, 53.2% of women giving birth were offered an HIV test; between 1996 and 2002, the rate had climbed to 84.2%. All in all, 96.9% of women with unknown HIV status accepted the HIV test [23].

A study conducted in Ontario, Canada by Remis et al., showed that by implementing a policy to offer HIV counselling and testing to all pregnant women in 1999, increased the testing rate from 33% in 1999 to 96% in 2010. The policy recommended an opt-in approach – HIV testing carried out with pre-test counselling and informed consent [22]. The Canadian province of Alberta uses an opt-out strategy for prenatal HIV screening. in 2002–2004, serum samples from women who opted-out were serologically tested for HIV. The proportion of specimens from women who opted out of prenatal HIV testing was low and decreased from 4.3% in 2002 to 3.6% in 2004. HIV seroprevalence among specimens from women who opted out was, however, 3.3 times higher than the HIV seroprevalence among specimens from women who opted-in during the study period [21].

A Canadian study by Dorval et al. among women attending antenatal care clinics in 2005, recruited prior to their first antenatal appointment, focused on how knowledge and attitudes regarding HIV and antenatal HIV screening influence screening rates. Most women (92%) supported universal HIV screening in the prenatal period; 72% agreed with an opt-out policy, and 24% preferred to opt-in. Women accepting prenatal HIV screening were more likely to be aware of the benefits of screening to reduce the MTCT rate [15].

A French study by Jasseron et al. investigated whether MTCT management and rate differed between African immigrants and French-born HIV type 1-infected women who gave birth in France in 1984–2007. The proportion of African mothers among HIV type 1-infected pregnancies increased from 11.8% in 1984–1986 to 45.4% in 1996–1998 and 64.0% in 2002–2004. A higher percentage of African women (40.6%) discovered their infection during pregnancy than French-born mothers (11.5%); 7.6% of the African women started antiretroviral therapy after 32 weeks gestation (versus 4.1% in French-born pregnant women). Late treatment initiation was associated with late access to HIV diagnosis and prenatal care. The overall MTCT rate among mothers receiving antiretroviral therapy during pregnancy was 1.5% in 1997–2004. The rate was higher in African (1.8%) than French-born women (0.8%) [18].

Data collected in Italy by Floridia et al. in 2001–2006 also indicated that foreign-born women were less likely to be aware of being HIV-infected before pregnancy (87.6% versus 52.1%); they also start antiretroviral treatment later (week 14 versus week 7) than women of Italian nationality. Seven cases of MTCT were observed (rate: 1.9%). The two cases in non-Italian women included one woman who was diagnosed after delivery and one woman diagnosed at delivery. The five cases in Italian women included four women who received treatment with antiretroviral drugs during pregnancy and one woman who received intra-partum treatment only [16]. The authors pointed out the need for specific interventions to increase counselling and HIV testing rates in foreign women before they become pregnant.

3.2.2 Cost-effectiveness of antenatal screening for HIV

Three cost-effectiveness analyses from the 2000s were identified (Table 1).

The cost-effectiveness of universal antenatal screening depends directly on the prevalence of HIV infection. In a 2008 study, universal screening in Amsterdam, the Netherlands, was considered cost-effective if the prevalence was equal to, or higher than, 14 cases per 100 000 population [24]; for Australia, prevalence for cost-effectiveness was needed to be at 4.37 cases per 100 000 population to reach cost-effectiveness [25]. A study from New Zealand cited the willingness of policy makers to pay for an additional life-year gained as an influence on decisions with regard to universal or selective screening [26].

In the Dutch study mentioned above, universal screening for HIV infections during pregnancy was compared to not offering screening at all [24]. The analysis was done from a healthcare perspective. The study estimated life years gained (LYG) by avoiding infections in children, as well as the costs associated with screening and lifetime medical costs of HIV-infected children. The study found systematic screening to be cost-effective as compared with no screening all, based on a willingness-to-pay threshold value of 20 000 EUR/LYG if the prevalence of HIV-infected pregnant women was at least 14 cases per 100 000 population. The authors concluded that universal HIV screening during pregnancy in Amsterdam was justified and generated significant net cost savings and health benefits in most situations.

In a 2004 Australian study, universal HIV screening during pregnancy was compared with the then-current practice of testing only if the pregnant woman explicitly asked to be tested or was considered to be at high risk [25]. The cost-effectiveness of systematic screening was assessed by looking at the likelihood of HIV infection among those not screened. The study estimated additional life years gained by mothers and children, the costs associated with screening, and the lifetime medical costs for HIV-infected children. The value of one additional year of life was defined as the average income per capita multiplied by two. Also taken into account were the costs of an earlier initiation of treatment for infected mothers and children and training costs for healthcare personnel. Universal HIV screening was estimated to be cost-effective in Australia if the prevalence of HIV infection among unscreened populations was between 0.0016% and 0.0106%. The authors concluded that universal screening would be cost-effective at a very low prevalence and would generate measurable benefits. They also highlighted the need for accurate statistics on prevalence.

An analysis from a healthcare point of view compared universal HIV screening of pregnant women in New Zealand with screening based on risk assessment [26]. In the analysis, treatment costs for mothers and children were included 'for a defined period after birth to a point when it was assumed that both mothers and babies would have been identified regardless of a universal screening programme' [26].

The additional life years gained by infected mothers with earlier initiation of treatment were also taken into account. The results of this analysis compared favourably with cost-estimates per life year gained from similar studies in other developed countries as well as to other healthcare interventions in New Zealand. The main factor affecting the decision of whether to implement universal screening programmes in New Zealand was HIV prevalence in addition to the policy makers' willingness to pay for an additional life-year gained.

Table 1. Economic assessment of HIV screening during pregnancy

Publication (country)	Comparator	Type of analysis, perspective, time factor, cohort, prevalence, test assumptions	Findings
HIV			
Rozenbaum et al. 2008 (Amsterdam, the Netherlands) [24]	No screening	• Cost effectiveness analysis • Healthcare • Children's lifespan • One-year cohort (about 10 000 pregnancies) • Prevalence 93 cases/100 000 population • Combined sensitivity and specificity of screening and confirmatory tests 100%	• Universal screening found 9.3 maternal infections yearly (93/100 000, number needed to screen: 1 075) and prevented infections in 2.4 children. • Total cost of the screening programme was EUR 376 408 (EUR 156 837/one child's infection avoided. • Lifetime medical costs for an HIV-infected child: EUR 179 974 • In sensitivity analyses, the incremental cost-effectiveness ratio for screening vs. no screening became positive when the number of new HIV cases decreased to less than 69/100 000. At a willingness to pay threshold of EUR 20 000/LYG screening remained cost-effective even at low incidence of new cases (up to 14/100 000).
Graves et al. 2004 (Australia) [25]	Current practice where test is conducted if an increased risk is identified or the mother wants to be tested	• Cost effectiveness analysis • Quasi-societal perspective* • Lifetime • One-year cohort (about 250 000 deliveries) • Analysed with different prevalence assumptions among the unscreened (67%) • Combined sensitivity and specificity of screening and confirmatory tests 100%	• Universal screening with prevailing practice is cost-effective if the prevalence of HIV cases among unscreened is at least 4.37/100 000, which is when universal screening can detect an additional 6.95 maternal infections per year and prevent 1.73 infections in children; each child would gain 46.97 additional years of life (LYG). Cost/LYG: AUD 39 000 (EUR 29 000). With higher prevalence, screening achieved net benefits.

Publication (country)	Comparator	Type of analysis, perspective, time factor, cohort, prevalence, test assumptions	Findings
HIV			
Bramley et al. 2003 (New Zealand) [26]	Screening based on risk mapping	• Cost effectiveness analysis • Healthcare • Lifetime • One-year cohort (about 56 000 pregnancies) • Prevalence 30/100 000	• Universal screening found 14.25 maternal infections per year (25.4/100 000, number needed to screen: 3 930) and prevented 1.15 infections in children which meant 41.97 life years gained (LYG). • Screening based on risk mapping found 8 maternal infections yearly and prevented 0.65 infections in children, with 19.98 LYG. • Incremental cost-effectiveness ratio for universal screening versus screening based on risk mapping was USD 267 944 (EUR 198 300)/one child's infection avoided and USD 7336 (EUR 5 400 EUR)/LYG.

** Quasi-societal perspective – the authors included costs and benefits to the state-funded healthcare sector and added a valuation of a life-year gained that reflects the preferences of individuals in the community.*

3.3 Hepatitis B

3.3.1 Effectiveness of antenatal screening for hepatitis B

The search did not identify any comparative studies on the effectiveness of antenatal screening for hepatitis B, but a total of six articles was found that dealt with the effectiveness of hepatitis B screening. A further three articles contained effectiveness data.

The effectiveness of antenatal screening for the prevention of hepatitis B vertical transmission was shown to depend on the prevalence of infection and the level of maternal viral load among pregnant women, as well as the coverage of the screening programme.

The effectiveness of antenatal screening for the prevention of perinatally transmitted HBV infection was assessed in six Italian regions in 2001. It was shown that 95% of all newborns of HBsAg-positive mothers were given active and passive immunisation; all newborns from foreign mothers received active and passive immunisation. The introduction of compulsory antenatal HBsAg screening for pregnant women led to vastly improved screening adherence. Three factors were observed to predict lack of compliance with screening: large family size, birth in a private hospital, and immigration from a developing country. Pregnant women from foreign countries with high HBsAg carrier rates were shown to be two times less likely to adhere to HBsAg screening than Italian women. Supplementary efforts were suggested to improve the effectiveness of the programme among foreign-born women [27].

Another Italian study evaluated compliance with a protocol for the prevention of perinatal hepatitis B infection in public and private hospitals of 13 Italian regions between 2008 and 2009. Prevalence of HBsAg among pregnant women varied between 0.4% (Italian-born women) and 3.44% (women born in eastern Europe); overall prevalence was 0.86%. Nearly 98% of pregnant women were screened and 100% of newborns from HBsAg-positive mothers received immunoprophylaxis at birth. Giving birth in a public hospital or in hospitals located in southern Italy and being of foreign nationality were predictors of not being screened [28].

In Denmark, selective screening missed 30–50% of pregnant women in high-risk groups while opt-out screening (introduced in 2005) led to a vaccination coverage of 96% among newborns of HBsAg-positive mothers, twice as high as before. The prevalence of hepatitis B in this study was 0.012% among women of Danish origin and 2.74% among foreign-born women. General screening prevented 8.4% cases of mother-to-child transmissions among newborns from mothers who carried the hepatitis B virus [29].

A study from Ireland found that the uptake of hepatitis B screening was excellent: 99.98% of women presenting for antenatal care accepted hepatitis B screening. Screening revealed that in 87% of cases the HBV carrier status was previously unknown. The cost of screening equated GBP 1 013 per new diagnosis, which was considered to be highly cost-effective considering the morbidity and mortality associated with vertically transmitted hepatitis B. Selective screening would have missed a significant number of those infected. Opt-out screening was concluded to be more appropriate than selective screening, with the added advantage of being equitable and easy to implement [30].

In Greece, the reasons for not complying with universal prenatal testing of HBsAg were studied as there were concerns that women with a higher disease burden may escape screening. Universal mass vaccination combined with improvements in socioeconomic and sanitary conditions, as well as screening of blood donors, led to a

significant decrease in HBV prevalence. A large influx of immigrants led to a shift in the epidemiology, with immigrant women comprising almost 20% of the child-bearing population in Greece. The overall screening rate was 91.3% in a nationwide study; a hospital in Athens serving a large population of refugees reported a rate of 89.4%. Pregnant women who escaped hepatitis B screening were more likely to be chronically infected, deliver in a public hospital, and be classified as 'illiterate immigrants'. It was concluded that stepped-up surveillance, immunisation programmes, and better access to routine screening was needed to effectively prevent MTCT among immigrant mothers [31].

Norway is classified as a low-prevalence country for hepatitis B infection; the prevalence of hepatitis B in pregnant women is 0.1%. Vaccination is targeted primarily at risk groups. National guidelines recommend the screening of immigrants from high-prevalence countries, particularly asylum seekers, but also children adopted from abroad. Data regarding the uptake of testing and vaccination among these populations are limited. The percentage of mother-to-child transmission of registered routes of transmission was shown to be 0.2%. It was concluded that universal screening should be introduced and that a universal vaccination strategy should be considered, given the high cost of reaching the target populations. The authors also recommend that the surveillance system for hepatitis B should be evaluated. In addition, screening effectiveness should be assessed and immigrant populations should receive vaccinations [32].

Since 1989, the Netherlands has screened all pregnant women for HBsAg at their first visit to the obstetrician, midwife or GP. A study from Amsterdam, where hepatitis B prevalence is higher than in the rest of the Netherlands, found an increase of 91% to 97% in antenatal screening coverage during 1993–1998. The rate of HBsAg positivity was lowest (0.07%) among pregnant women from the Netherlands Antilles, low (0.07%) among native Dutch women, and highest (8.9%) among women from Ghana. The Amsterdam enhanced screening programme was considered cheap and effective and was used to monitor the impact of neonatal immunisation. The programme included the analysis of samples in the public health laboratory, which then informed the municipal health services if HBsAg-positive mothers needed confirmatory testing. The expected delivery date was recorded in a computerised system, and a public health nurse made sure that hepatitis B immune globulin (HBIG) was available. Within a week the public health nurse verified that HBIG was given and arranged for the first dose of vaccine to be administered at home or in the hospital; the second dose of vaccine was administered at a municipal health services site [33]. It was suggested that contact tracing and the vaccination of contacts of HBsAg-positive women should be integrated into the hepatitis B antenatal screening programme after encouraging results in reducing the pool of infective individuals among older children and adults [34]. In 2008, the antenatal HBsAg prevalence for the Netherlands was 0.33%, with 99.2% of the HBsAg-positive women being long-term carriers. The most frequently reported regions of origin were Asia (38%) and sub-Saharan Africa (23%). Due to antenatal screening, an estimated number of 50 to 75 HBV infections in newborns could be prevented annually [7].

3.3.2 Cost-effectiveness of antenatal screening for hepatitis B

The literature search identified three cost-effectiveness analyses from the 1990s on hepatitis B screening (Table 2).

Two studies were from an UK healthcare perspective. Prevalence ranged from 0.083% to 1.3%. The studies compared universal screening of pregnant women with screening based on risk mapping [35,36]. Both concluded that the cost-effectiveness of universal screening was at an acceptable level and recommended that screening should be introduced. The studies highlighted that limiting screening to high-risk groups would leave a number of maternal infections undetected and lead to the infection of children. The most important assumptions that affected the results of the sensitivity analyses were infection prevalence, the cost of screening tests, and the likelihood of transmission.

A study from the Belgian healthcare perspective compared universal screening with no screening at all. Prevalence at the time of the study was 0.67%. [37]. The cost-effectiveness of universal screening was comparable to other generally accepted medical procedures. Screening all pregnant women and vaccinating all neonates at risk was not considered cost-saving. The main assumptions influencing the results of the sensitivity analyses were the prevalence of infection, screening and vaccination costs, and discount rate.

Table 2. Economic assessment of hepatitis B screening during pregnancy

Publication (country)	Comparator	Type of analysis, perspective, time factor, cohort, prevalence, test assumptions	Findings
Hepatitis B			
Jordan & Law 1997 (UK) [35]	Screening based on identified high risk	• Cost effectiveness analysis • Healthcare • Lifetime • Cohort size: 100 000 • HBsAg+: the entire population 152/100 000, high-risk populations 500–3000/100 000 • Proportion of HBeAg-positive people in the entire population: 21%, in high-risk populations: 17–40% • Sensitivity and specificity of screening tests 100%.	• Universal screening found 152 carrier mothers in a cohort of 100 000 (number needed to screen: 4 000), prevents 34 newborn infections and 6 deaths in children due to hepatoma or chronic liver disease. Four children were infected in spite of systematic screening. • Universal screening program costs: GBP 150 000 (GBP 4412 or EUR 5 300/one child's infection avoided and GBP 2 500 or EUR 3 000/LYS when screened in every pregnancy); GBP 78 000 (GBP 2 294 or EUR 2 750 EUR/one child's infection avoided, and GBP 1 300 or EUR 1 560/LYS) when screened only in the first pregnancy. • Screening based on identified high risk identified 102 carrier mothers, preventing 24 infections in children and 4.3 deaths; 14 children were infected. The cost was GBP 330 or EUR 400 EUR/LYS when screened only in the first pregnancy.
Dwyer & McIntyre 1996 (East Anglia, UK) [36]	Screening based on identified risk (current practice)	• Cost effectiveness analysis • Healthcare • Lifetime • One year cohort (approximately 26 500 pregnancies) • HBsAg+: 83/100 000 • HBeAg-positive: 22% • Sensitivity of screening test: 100%; specificity prior to the confirmatory test 99.5%.	• Universal screening found 22 carrier mothers per year and 4.4 children. • Screening based on identified risk found 7 carrier mothers (32%) and prevented infection in 1.8 children. • Universal screening prevented 2.6 infections and 0.8 deaths of children, saving 21 life years (LYS) as compared to current practice. • Direct costs of universal screening: GBP 51 560 (GBP 11 718 or EUR 14 000/one child's infection avoided); the incremental cost /LYS was GBP 2 437 (EUR 2 912).
Tormans et al. 1993 (Belgium) [37]	No screening	• Cost effectiveness analysis • Healthcare • Lifetime • Cohort size: 100 000 • HBsAg+: 670/100 000 • HBeAg-positive: 20%	Universal screening found 670 carrier mothers, prevented 175 infections of the children, and saved 42.7 life years (LYS) per 100 000 pregnant women screened. • Despite this screening, 26 children were infected. • Without screening, 201 children would have been infected. • Savings in medical costs for 175 avoided infections were BEF 6 013 129. • The screening programme had a total cost of BEF 31 719 490 (BEF 181 254 or USD 5 850/one child's infection avoided), the net cost to society was 24 918 903 BEF (142 394 BEF or 4 593 USD/one child's infection avoided and BEF 583 581 or USD 18 825/LYS).

3.4 Syphilis

3.4.1 Effectiveness of antenatal screening for syphilis

The literature search did not identify any comparative studies on the effectiveness of antenatal screening for syphilis, but five articles reporting on the effectiveness of syphilis screening were identified. A further five articles were included from other searches. Screening proved to reduce adverse pregnancy outcomes (i.e. stillbirth and perinatal death) and although women from country-specific high-risk groups were found to be affected by higher rates of syphilis during pregnancy, a universal antenatal screening policy was considered effective and ethically appropriate.

A 2006 study from the United Kingdom cited three major risk factors for infectious syphilis in pregnant women included: living in London and the South East, belonging to an ethnic minority group, and having been born abroad. Antenatal screening was performed routinely, but there were no national data on the number of cases of syphilis diagnosed during pregnancy; also lacking were data on the rate of congenital syphilis. The study called for robust national surveillance of syphilis in pregnant women and the identification and recording of cases of congenital syphilis [38].

In the United States, syphilis was found to be most common in non-white women below 30 years of age, with little education and low income. Women with syphilis were more likely to have late or no prenatal care. Women at high risk or in high-prevalence areas were recommended to be screened a second time in the third trimester [39].

An Austrian study documented the development of syphilis and analysed the effectiveness of antenatal syphilis screening practices in Austria. In Austria, the incidence of syphilis had declined, and the geographical variation was large. In metropolitan Vienna, the incidence was 12 times higher than in the federal provinces, which are mainly rural in character. The cost of screening in rural areas was four times higher than the potential savings. Calculations suggested that universal syphilis screening in pregnancy was not justified. The authors recommended that consideration should be given to replace general screening with targeted screening for high-risk groups [40].

In a 2011 systematic review of literature, three outcomes were assessed to examine evidence for the effectiveness of interventions: increased uptake of syphilis testing, increased treatment rates, and reduction in adverse pregnancy outcomes. Ten studies with interventions to improve outcomes of antenatal syphilis screening were included. The studies did not allow for the assessment of the ideal time for syphilis screening. The included studies did not provide sufficient information on the outcomes of partner treatment; also lacking was sufficient information on repeat screenings during the third trimester to reduce the risk of reinfection. Delayed treatment of syphilis in pregnancy increased the likelihood of congenital syphilis. Screening was found to reduce adverse pregnancy outcomes, particularly rates of stillbirth and perinatal death [41].

In Switzerland, antenatal screening for syphilis was not generally recommended; it was discontinued during the 1990s. Notifiability of syphilis infections was restored in 1999 due to increasing incidence rates. From 2006 to 2009, infectious syphilis cases in women of childbearing age increased substantially. Improvements in prenatal care and syphilis programmes ware recommended [42].

A WHO analysis of global and regional estimates of syphilis in pregnancy and adverse outcomes was performed for 2008 data. Syphilis seropositivity among antenatal care attendees in Europe was reported to be 0.16%. The analysis included only a few countries for which data reported through the HIV Universal Access system were available. It was recommended that all countries should collect data on at least three indicators of MTCT of syphilis: proportion of antenatal care attendees that are tested for syphilis, proportion of seropositive attendees, and proportion of seropositives that are adequately treated. It was concluded that all countries should scale up the screening and treatment for syphilis in pregnancy [43].

In 1999, the compulsory notification of syphilis came to an end in the Netherlands. Since then there had been no nationwide registration system for the monitoring of congenital syphilis. Acceptance of syphilis screening tests was high; tests were only refused between one and four times a year. Congenital syphilis was diagnosed in fewer than five newborns per year; in all cases the mothers belonged to vulnerable groups (illegal immigrants or drug users). It was estimated that 10 cases of syphilis in newborns were prevented by screening. Universal screening was considered simpler and more acceptable than a programme only focused on risk groups [7].

A prospective Italian study from 2006–2007 found the maternal syphilis seroprevalence at delivery to be 0.17%. Most seropositive mothers were born outside Italy, but foreign origin was not associated with a worse neonatal outcome. Congenital syphilis was diagnosed in 20/100 000 live births. Maternal risk factors included young age (<20), no antenatal care, and no adequate treatment. The authors did not observe any association with marital status, unemployment, previous syphilis diagnosis or coexistence of other maternal infections. The majority of infants born to seropositive mothers was delivered in northern Italian hospitals from immigrant mothers mostly from eastern Europe. A total of 25% of Italian mothers had no antenatal syphilis screening versus 12% of immigrant women [44].

In a UK study from the late 1990s, switching to targeted surveillance or even stopping antenatal screening for syphilis was observed to save relatively little money. Three groups of pregnant women were identified as potential target groups: pregnant women in the Thames region, women belonging to non-white ethnic groups, and women born outside the United Kingdom. Selective screening by country of birth or ethnic group would detect at least 70% of cases; targeting by region would also be effective, but up to 30% of cases would still be missed. In addition, selective screening would cause ethical and medico-legal problems and be politically and practically difficult. Medico-legal costs could be associated with failure to prevent miscarriages, stillbirths and illness resulting from congenital infection because of missed cases. Targeted screening runs the risk of missing newly developing risk groups and unexpected increases in transmission [45].

In an article without primary data, the authors advocated a priority listing for scaling up control over sexually transmitted infections other than HIV/AIDS. The strengthening of partner notifications was also considered necessary, which would improve case finding, would prevent re-infection from an existing partner, and could interrupt the onward transmission in a sexual network [46].

3.4.2 Cost-effectiveness of antenatal syphilis screening

Two cost-effectiveness analyses were identified for the syphilis review (Table 3).

A literature search on economic evaluations of syphilis screening retrieved a cost-effectiveness analysis from a healthcare perspective (late 1990s, United Kingdom) [45] and a cost–benefit analysis using the societal point of view from (early 1980s, Norway [47] (Table 3). Both recommended that syphilis screening in early pregnancy should be continued.

The UK study [45] compared systematic screening for syphilis in early pregnancy to other more limited screening options. The consequences of infection transmission to the child (impact on life expectancy, treatment and other costs) were not estimated. The study found that direct costs for the limited screening options were lower, but only 70 to 77% of infected mothers would be identified, i.e. several children would be infected each year. Limiting screening would also bring ethical, legal, practical and political problems. For these reasons and due to the changing international syphilis prevalence, it was recommended that systematic screening during pregnancy should be implemented.

In the Norwegian study [47], systematic screening for syphilis in early pregnancy was compared to no screening at all. Screening was estimated to avert costs caused by infections in children (i.e. treatment, special education, residential care and loss of earnings), and the achieved cost savings were almost four times higher than the costs incurred by the yearly screening programme. Continuation of the screening was recommended.

A WHO study modelling the costs and cost-effectiveness of screening and treatment of syphilis during pregnancy was published when this report was almost finalised. It modelled screening in eight generic country scenarios and concluded that congenital syphilis could be eliminated through an expanded screening and treatment programme in antenatal care facilities. This would be cost saving in high-prevalence settings where prevalence of a reactive syphilis serological test in pregnancy is 3%. In the low-prevalence scenarios, the cost per DALY (disability-adjusted life year) averted ranged from USD 24 to USD 111; the authors concluded that according to the WHO standards this would be cost-effective [48].

Table 3. Economic assessment of syphilis screening during pregnancy

Publication (country)	Comparator	Type of analysis, perspective, time factor, cohort, prevalence, test assumptions	Findings
SYPHILIS			
Connor et al. 2000 (UK) [45]	Limited screening options (geographical areas, screening of different risk groups)	• Cost effectiveness analysis • Healthcare • About one year • One year cohort (about 750 000 pregnancies) • Prevalence in systematic screening 6/100 000, in limited groups from 18 to 62 /100 000 • Combined sensitivity and specificity of screening and confirmatory tests 100%.	• Systematic screening found 40.3 maternal infections yearly (number needed to screen: 18 of 602) and prevented 13.5 infections in newborns. Cost: GBP 49 928 (EUR 59 900)/one child's infection avoided. • Restricted screening options found 28.3–31 maternal infections and prevented 8.9–9.8 infections in children. Cost: GBP 8 958–20 976 (EUR 10 749–EUR 25 170)/one child's infection avoided. • Incremental cost-effectiveness ratio of systematic screening versus limited screening options: GBP 109 588–GBP 153 461 (EUR 131 500–EUR 184 150)/one child's infection avoided.
Stray-Pedersen 1983 (Norway) [47]	No screening	• CBA • Societal • Children's lifespan • One year cohort (about 50 000 pregnancies) • Prevalence 20/100 000 • Combined sensitivity of screening and confirmatory tests 100%, combined specificity 99.6%.	• Systematic screening found 10 maternal infections annually (20/100 000, number needed to screen: 5 000) and prevented six infections in children/50 000 pregnancies. Cost of the programme: USD 230 000 (USD 38 300 or EUR 28 800 EUR/one child's infection avoided). • The economic value of benefits achieved by screening (avoiding institutional care, special education, and loss of income): USD 877 920. Benefit to cost ratio: 3.8.

3.5 Rubella susceptibility

3.5.1 Effectiveness of antenatal screening for rubella susceptibility

The literature search did not identify any comparative studies on the effectiveness of antenatal screening for rubella susceptibility. However, seven descriptive studies concerning the effectiveness of rubella susceptibility screening were identified.

In some countries with high vaccination coverage and low rubella incidence, antenatal screening of rubella susceptibility has been discontinued. However, subnational areas and risk groups remain where antenatal screening for rubella susceptibility is still considered necessary [49].

Three UK studies assessed the effectiveness of rubella susceptibility screening. In a study from London, a high screening rate of over 90% for rubella susceptibility was found, with an overall rubella susceptibility of 3.6%. However, in some areas of London the susceptibility rates were considerably higher (14.3%), which was understood to reflect the ethnic diversity of these areas [50]. In a study conducted by the National Health Service (NHS) Blood and Transplant, a large number of samples from antenatal women was screened during routine checks. The NHS study identified two predictors of low levels of rubella antibodies: birth cohorts born after 1990 and ethnicity [51]. A significant increase in those with low levels of rubella antibodies (< 10IU/ml) was observed in another UK study. A changing pattern of rubella seronegativity and susceptibility in pregnant women born before and after 1983 was observed. It was found difficult to obtain accurate figures for uptake for postpartum immunisation rates because there was no requirement to notify adult measles, mumps and rubella (MMR) vaccinations to a recording authority [52].

In Ireland, researchers concluded that in order to prevent congenital rubella syndrome (CRS) health services should focus on women who are young, nulliparous, and born outside the EU. The increased rate of rubella seronegativity in the general population in 2009 was associated with an increase in migration. The study also found that it would be cost-effective to focus screening on this easily identifiable group. Also, vaccinations without serological testing for women from countries without rubella programmes could be cost-effective [53].

In a Canadian study from Quebec, in-hospital postpartum vaccination was found to be an effective means of vaccinating groups at risk. Misconceptions about vaccine use were noted that affected timely administration and led to missed opportunities [54].

In Italy, free serological testing for rubella susceptibility has been part of the standard pregnancy care since 1995. A study on congenital infections from the Campania region found that no systematic process and outcome monitoring was implemented. Standards of care were unequal, possibly excluding low-income pregnant women with poor or no antenatal care. The dramatic rise in congenital rubella and rubella incidence during pregnancy in 2008 might have been a consequence of the vaccination campaigns for children in 2004–2007 that were carried out without conducting a catch-up campaign to vaccinate susceptible women of childbearing age. Congenital rubella was found to be an issue since all but one case were found in native-born mothers. Actions to reduce the gap between children and adult vaccination coverage were recommended [55]. The goals of the National Program to Eradicate Measles and Congenital Rubella (PNEM) in Italy were to reduce and limit the occurrence of CRS to less than one case per 100 000 live births (fewer than five cases per year), to reach 95% vaccination coverage in paediatric age, and to have less than 5% of pregnant women susceptible to rubella. The proportion of women found to be at risk of rubella infection was 14.2%. The highest risk rate was found in women in the 15–25-year-old group (24.7%); 33.8% of susceptible women had been pregnant at least once before. Vaccination was recommended to be performed before discharge. A high proportion of women was observed to be unaware of the risk posed by rubella infection during pregnancy (36%) [56].

3.5.2 Cost-effectiveness of antenatal screening for rubella susceptibility

Only one cost-effectiveness analysis about rubella susceptibility screening was identified in the literature search (Table 4).

The Dutch cost-utility analysis from 2010 [49] compared screening non-vaccinated pregnant women in the low-vaccination-coverage regions (LVR), screening all pregnant women in LVR, and screening all non-vaccinated pregnant women in the country. The calculations were based on the 2004–2005 rubella epidemic in the Netherlands, and costs were calculated separately for epidemic and non-epidemic years. Screening pregnant women for rubella antibodies was found cost-effective if targeted at unvaccinated women in LVR in the Netherlands. Screening all pregnant women in LVR or screening all non-vaccinated pregnant women in the Netherlands was cost-effective if cost savings due to avoided treatment costs for prevented complications were lifelong.

Table 4. Economic assessment of rubella screening for susceptibility during pregnancy

Publication (country)	Comparator	Type of analysis, perspective, time factor, cohort, prevalence, test assumptions	Findings
Rubella			
Lugner et al. 2010 (Netherlands) [49]	Screening based on vaccination status	• Cost-utility analysis • Healthcare • Lifetime • Screening time frame: 16 years • 2004–2005 outbreak, pregnant women with rubella infection: 32 cases, congenital rubella syndrome: 11 cases	• The annual expected costs of screening: (1) all non-vaccinated pregnant women in LVR: EUR 17 900, (2) screening all pregnant women in LVR: EUR 107 800; and (3) screening all non-vaccinated pregnant women: EUR 266 600. • Preventing a complications of rubella infection during pregnancy leads to an average of 22.9 QALYs gained. • The screening and vaccination programme during lifelong scenarios 2 and 3 would have a cost-effectiveness ratio between EUR 26 900 and EUR 28 100/QALY gained. • The 16-year period would be cost-effective if targeted at non-vaccinated women in LVR (EUR 1 100/QALY gained).

Note: The cost-utility analysis was focused on three scenarios: (1) screening non-vaccinated pregnant women in low-vaccination-coverage regions (LVR); (2) screening all pregnant women in LVR; (3) screening all non-vaccinated pregnant women in the Netherlands (including pregnant first-generation non-Western immigrant women).

3.6 Risk of bias and quality/strength of evidence

The included studies on the effectiveness of antenatal screening on HIV, hepatitis B, syphilis and rubella susceptibility were in general descriptive and did not include a comparison group and were thus judged to be of low quality [1].

The three studies on the cost-effectiveness of HIV screening [24-26] were of high quality (Table 5). They fulfilled all [24], 9/10 [25] or 8/10 [26] of the 10 criteria for programme cost-effectiveness studies (see Drummond and Jefferson [2]). The description of the comparator (ordinary care) was not described in full detail in the two latter studies [24,25], and Bramley et al. [26] had not reported capital costs of the programme. These omissions were judged not to impact on the validity of the conclusions.

Cost-effectiveness studies on screening for hepatitis B [35-37] were of high quality, fulfilling at least 7 of the 10 Drummond criteria [2] (Table 5). None of the studies discussed generalisability with regard to other settings or presented an incremental analysis, and only one [37] used discounting in presenting the effects. These omissions were judged not to impact on the validity of the conclusions. Two of the cost-effectiveness studies [45,48] fulfilled all Drummond criteria and were thus of high quality (Table 5). Stray-Pedersen [47] failed to conduct incremental and sensitivity analyses, and the conclusions were based on calculated net benefit rather than cost–effectiveness ratio, but the quality of the study was still considered to be high.

The cost–utility study on rubella susceptibility screening fulfilled all Drummond criteria [2] (Table 5).

Table 5. Quality assessment of the selected publications based on the Drummond criteria for economic evaluations

	HIV			Hepatitis B		Syphilis		Rubella	
Quality assessment of included programme cost-effectiveness studies (Drummond criteria)	Rosenbaum et al., 2008	Graves et al., 2004	Bramley et al., 2003	Jordan & Law, 1997	Dwyer & McIntyre, 1996	Tormans et al., 1993	Connor et al., 2000	Stray-Pedersen, 1983	Lugner et al., 2009
1. Was a well-defined question posed in answerable form?	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
1.1. Did the study examine both costs and effects of the service(s) or programme(s)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.2. Did the study involve a comparison of alternatives?	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
1.3. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?	**Yes**	**No**	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
2.1. Were there any important alternatives omitted?	Yes	Yes	Yes	No	No	Yes	No	Yes	No
2.2. Was (should) a do-nothing alternative be considered?	No	No	No	No	No	Yes	Yes	Yes	No
3. Was the effectiveness of the programme or services established?	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
3.1. Was this done through a randomised, controlled clinical trial?	No	No	No	No	No	No	No	No	No
3.2. Was effectiveness established through an overview of clinical studies?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3.3. Were observational data or assumptions used to establish effectiveness?	No	Yes	Yes	No	Yes	No	Yes	Yes	No
4. Were all the important and relevant costs and consequences for each alternative identified?	**Yes**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
4.1. Was the range wide enough for the research question at hand?	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
4.2. Did it cover all relevant viewpoints?	No	No	No	Yes	Yes	No	No	No	Yes
4.3. Were the capital costs, as well as operating costs, included?	Yes	Yes	No	No	No	No	Yes	No	Yes
5. Were costs and consequences measured accurately in appropriate physical units?	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
5.1. Were any of the identified items omitted from measurement?	No	No	Yes	No	No	No	No	No	No
5.2. Were there any special circumstances that made measurement difficult and were these handled appropriately?	No	No	Yes	No	No	No	No	No	No
6. Were the cost and consequences valued credibly?	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
6.1. Were the sources of all values clearly identified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6.2. Were market values employed for changes involving resources gained or depleted?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6.3. Where market values were absent or did not reflect actual values, were adjustments made to approximate market values?	No	No	No	No	No	No	No	No	No
6.4. Was the valuation of consequences appropriate for the question posed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Were costs and consequences adjusted for differential timing?	**Yes**	**Yes**	**Yes**	**No**	**No**	**Yes**	**No**	**Yes**	**Yes**
7.1. Were costs and consequences that occur in the future 'discounted' to their present values?	No	Yes	Yes	No	No	Yes	No	Yes	Yes
7.2. Was justification given for the discount rate used?	No	No	No	No	No	No	No	Yes	No

	HIV			Hepatitis B		Syphilis		Rubella	
Quality assessment of included programme cost-effectiveness studies (Drummond criteria)	Rosenbaum et al., 2008	Graves et al., 2004	Bramley et al., 2003	Jordan & Law, 1997	Dwyer & McIntyre, 1996	Tormans et al., 1993	Connor et al., 2000	Stray-Pedersen, 1983	Lugner et al., 2009
8. Was an incremental analysis of costs and consequences of alternatives performed?	**Yes**	**Yes**	**Yes**	**No**	**No**	**No**	**Yes**	**No**	**Yes**
8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?	Yes	Yes	Yes	No	No	No	Yes	No	Yes
9. Was allowance made for uncertainty in the estimates of costs and consequences?	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**Yes**
9.1. If data on costs and consequences were stochastic, were appropriate statistical analyses performed?	Yes	Yes	Yes	Yes	Yes	Yes	yes	No	Yes
9.2. If a sensitivity analysis was employed, was justification provided for the range of values?	Yes	No	No	Yes	No	Yes	No	No	Yes
9.3. Were the study results sensitive to changes in the values?	No	Yes	Yes	Yes	Yes	Yes	Yes	-	Yes
10. Did the presentation and discussion of study results include all issues of concern to users?	**Yes**	**Yes**	**Yes**	**No**	**No**	**No**	**Yes**	**No**	**Yes**
10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)?	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
10.2. Were the results compared with those of others who have investigated the same question?	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No
10.3. Did the study discuss the generalisability of the results to other settings and patient groups?	No	Yes	No	No	No	No	No	Yes	Yes
10.4. Did the study allude to, or take account of, other important factors in the choice or decision under consideration?	No	Yes	Yes	Yes	No	No	Yes	No	Yes
10.5. Did the study discuss issues of implementation, and whether any freed resources could be redeployed to other programmes?	No	Yes	No	No	Yes	No	Yes	Yes	Yes

4 Discussion

The effectiveness of antenatal screening for each of the target infections depends primarily on the coverage of the screening programme, the quality of testing, and the effectiveness of treatment. In addition to these factors, cost-effectiveness is influenced by the prevalence of these infections among pregnant women, the cost of the screening programme, and the practice/policy that the screening is compared with. Programme costs depend mainly of the cost of administering and analysing the screening/confirmatory tests, the type of healthcare personnel and their time, cost of medication and other necessary treatment, and patient compliance.

Coverage and compliance with a universal screening policy can be enhanced by increasing the level of awareness through public information; enhancing provider awareness; improved access to testing, treatment and follow-up; and allocation of adequate resources [55]. Screening is usually only provided once (in the early stages of pregnancy). A second screening late during the pregnancy is highly unlikely to be cost-effective, especially in countries with relatively low incidence of HIV, HBV and syphilis. In general, universal screening is considered simpler and more acceptable than a programme which focuses on risk groups [7].

4.1 Limitations

The literature review for effectiveness and cost-effectiveness of antenatal screening was limited to publications in English or Nordic languages. Overall linguistic bias was low as only 29 (3%) of the 981 identified publications were excluded because of language restrictions. References to documents in other languages were preserved (but are not yet translated) in the source material for this project for potential future use.

The literature review on the cost-effectiveness of antenatal screening found relatively few relevant articles (three on HIV, three on hepatitis B, two on syphilis and one for rubella susceptibility). This emphasises the fact that antenatal screening for infectious diseases has rarely been assessed for cost effectiveness in an evidence-based manner. It also shows the need for an assessment of the existing practices. The scope of the literature search was broadened because the authors of this report felt that making recommendations based on only nine articles (and data collected from the survey) was inadequate. This allowed for the review of cost-independent factors of effectiveness at the operational level. The expanded search resulted in the inclusion of 19 additional articles on HIV, six on hepatitis B, five on syphilis and seven on rubella susceptibility screening, which provided helpful background information for the development of a future guidance document.

Literature reviews depend on the quality of search strategies and on the ability to identify all relevant articles that address the questions under review. Screening the search results for relevance always involves a degree of subjectivity, even when performed in accordance with predefined inclusion criteria. The selection of articles followed predefined steps and was always carried out by two persons who initially worked independently. Several search strategies were tested in the various databases, and the final search strategies were decided upon when no additional significant publications could be retrieved by further modifications to the algorithms.

It was particularly difficult for the project to comprehensively identify grey literature (reports and other types of publications not indexed in databases), even if published in English or one of the Nordic languages. Ancestry searches were used to identify such materials. Although this approach provided a few additional publications, it is likely that some relevant materials may have been missed.

5 Conclusions

With regard to HIV, hepatitis B and syphilis, most studies suggest that comprehensive, population-based antenatal screening is cost-effective in all European settings where this has been researched.

In the end, any judgement on cost effectiveness will be a value judgement. Judging whether a preventive programme is cost-effective is highly dependent on the thresholds set for the cost per life years (or other health metrics used) that can be saved, unless it can be shown that the programme actually is saving costs. This figure (which describes how much has to be invested in a program/intervention per year and for every life year saved) will vary between countries, depending on multiple factors that cannot be determined by any other authority than national policymakers because every country needs to prioritise its health investments in accordance with national needs. What is considered as 'tolerable costs' varies widely in Europe and can be somewhere between thousands and hundreds of thousands of euros per life year saved. In addition, comparisons of costs and cost-effectiveness thresholds are notoriously difficult between countries and systems, if not impossible, due to the heterogeneity of healthcare systems and the different approaches employed in the antenatal screening for infections.

The effectiveness of antenatal screening depends on the coverage of the screening programme, the quality of testing, and the effectiveness of treatment. The ability to reach all pregnant women, the sensitivity of the screening test (i.e. the capacity to identify all infected women), and the preventive treatment received by all infected pregnant women are factors that influence effectiveness.

In order to assess the performance (effectiveness) of antenatal screening for infections, it is essential to have comprehensive surveillance systems in place that accurately record prevention failures (i.e. the transmission of HIV, hepatitis B, syphilis or rubella from the mother to the child) and document the targets and indicators of all screening programmes. Ideally, surveillance systems record information from infected mothers *and* their children (in an attempt to identify risk factors for MTCT), document MTCT rates, identify targets and indicators, and point toward opportunities for improvement of antenatal screening and care.

6 Next steps

The results of this literature review will serve as a basis for an ECDC guidance document on strengthening antenatal screening programmes in the EU/EEA Member States.

References

1. Guyatt G, Rennie D, O'Meade M, DJ C. Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice. 2nd Edition ed. Chicago: American Medical Association; 2008.
2. Drummond MF, Sculpher MJ, Torrance GW. Critical assessment of economic evaluation. In: Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL, editors. Methods for the economic evaluation of healthcare programmes. 3rd ed. Oxford: Oxford University Press; 2005.
3. E European Centre for Disease Prevention and Control. Antenatal screening for HIV, hepatitis B, syphilis and rubella susceptibility in the EU/EEA. Stockholm: ECDC; 2016.
4. Surcel HM, Haula T, Mäkelä M, Aho I, Hiltunen-Back E, Salo E, et al. Screening for infections in early pregnancy in Finland. THL Report. 2014;7.
5. Naver L, Lindgren S, Belfrage E, Gyllensten K, Lidman K, Gisslen M, et al. Children born to HIV-1-infected women in Sweden in 1982-2003: trends in epidemiology and vertical transmission. J Acquir Immune Defic Syndr. 2006 Aug 1;42(4):484-9.
6. Rasmussen MB, Rasmussen JB, Nielsen VR, Herlin T, Fisker N, Hornstrup MK, et al. [Prevention of vertical transmission of HIV in Denmark]. Ugeskrift for laeger. 2008 Aug 18;170(34):2567-70.
7. Op de Coul EL, Hahne S, van Weert YW, Oomen P, Smit C, van der Ploeg KP, et al. Antenatal screening for HIV, hepatitis B and syphilis in the Netherlands is effective. BMC Infect Dis. 2011;11:185.
8. Hughes CA, Zuk D, Foisy M, Robinson J, Singh AE, Houston S. Prenatal screening and perinatal HIV transmission in Northern Alberta, 1999-2006. Am J Public Health. 2009 Oct;99 Suppl 2:S412-6.
9. Centers for Disease C, Prevention. Achievements in public health. Reduction in perinatal transmission of HIV infection--United States, 1985-2005. MMWR Morb Mortal Wkly Rep. 2006 Jun 2;55(21):592-7.
10. Birkhead GS, Pulver WP, Warren BL, Klein SJ, Parker MM, Caggana M, et al. Progress in prevention of mother-to-child transmission of HIV in New York State: 1988-2008. J Public Health Manag Pract. 2010 Nov-Dec;16(6):481-91.
11. Peters V, Liu KL, Dominguez K, Frederick T, Melville S, Hsu HW, et al. Missed opportunities for perinatal HIV prevention among HIV-exposed infants born 1996-2000, pediatric spectrum of HIV disease cohort. Pediatrics. 2003 May;111(5 Pt 2):1186-91.
12. Patterson KB, Leone PA, Fiscus SA, Kuruc J, McCoy SI, Wolf L, et al. Frequent detection of acute HIV infection in pregnant women. Aids. 2007 Nov 12;21(17):2303-8.
13. Boer K, Smit C, van der Flier M, de Wolf F, group Acs. The comparison of the performance of two screening strategies identifying newly-diagnosed HIV during pregnancy. Eur J Public Health. 2011 Oct;21(5):632-7.
14. Centers for Disease Control and Prevention (CDC). HIV testing among pregnant women – United States and Canada, 1998-2001. MMWR Morb Mortal Wkly Rep. 2002 Nov 15;51(45):1013-6.
15. Dorval V, Ritchie K, Gruslin A. Screening HIV in pregnancy: a survey of prenatal care patients. Can J Public Health. 2007 Sep-Oct;98(5):379-82. 2007 Sep-Oct;98(5):379-82.
16. Floridia M, Tamburrini E, Bucceri A, Tibaldi C, Anzidei G, Guaraldi G, et al. Pregnancy outcomes and antiretroviral treatment in a national cohort of pregnant women with HIV: overall rates and differences according to nationality. BJOG. 2007 Jul;114(7):896-900. Epub 2007 May 15.
17. Goldberg D, Logan L. Unlinked anonymous testing indicates antenatal HIV testing in England and Scotland is being successfully implemented. Euro Surveill. 2005 May 19;10(5):E050519.4.
18. Jasseron C, Mandelbrot L, Tubiana R, Teglas JP, Faye A, Dollfus C, et al. Prevention of mother-to-child HIV transmission: similar access for sub-Sahara African immigrants and for French women? Aids. 2008 Jul 31;22(12):1503-11.
19. Nielsen VR, Valerius NH. [HIV screening in pregnancy--too many failures?]. Ugeskrift for laeger. 2002 Nov 18;164(47):5522-4.
20. Perez K, Blanch C, Casabona J, Almeda J, Coll O, Cobemb. Coverage of HIV testing among pregnant women in Catalonia, Spain: a comparison of self-reporting with medical records. Eur J Public Health. 2004 Sep;14(3):261-6.
21. Plitt SS, Singh AE, Lee BE, Preiksaitis JK. HIV seroprevalence among women opting out of prenatal HIV screening in Alberta, Canada: 2002-2004. Clin Infect Dis. 2007 Dec 15;45(12):1640-3.

22. Remis RS, Merid MF, Palmer RW, Whittingham E, King SM, Danson NS, et al. High uptake of HIV testing in pregnant women in Ontario, Canada. PloS one. 2012;7(11):e48077.

23. Sarnquist CC, Cunningham SD, Sullivan B, Maldonado Y. The effectiveness of state and national policy on the implementation of perinatal HIV prevention interventions. Am J Public Health. 2007 Jun;97(6):1041-6.

24. Rozenbaum MH, Verweel G, Folkerts DK, Dronkers F, van den Hoek JA, Hartwig NG, et al. Cost-effectiveness estimates for antenatal HIV testing in the Netherlands. Int J STD AIDS. 2008 Oct;19(10):668-75.

25. Graves N, Walker DG, McDonald AM, Kaldor JM, Ziegler JB. Would universal antenatal screening for HIV infection be cost-effective in a setting of very low prevalence? Modelling the data for Australia. J Infect Dis. 2004 Jul 1;190(1):166-74.

26. Bramley D, Graves N, Walker D. The cost effectiveness of universal antenatal screening for HIV in New Zealand. Aids. 2003 Mar 28;17(5):741-8.

27. Stroffolini T, Bianco E, Szklo A, Bernacchia R, Bove C, Colucci M, et al. Factors affecting the compliance of the antenatal hepatitis B screening programme in Italy. Vaccine. 2003 Mar 7;21(11-12):1246-9.

28. Spada E, Tosti ME, Zuccaro O, Stroffolini T, Mele A; Collaborating Study Group. Evaluation of the compliance with the protocol for preventing perinatal hepatitis B infection in Italy. J Infect. 2011 Feb;62(2):165-71.

29. Harder KM, Cowan S, Eriksen MB, Krarup HB, Christensen PB. Universal screening for hepatitis B among pregnant women led to 96% vaccination coverage among newborns of HBsAg positive mothers in Denmark. Vaccine. 2011 Nov 21;29(50):9303-7.

30. Healy CM, Cafferkey MT, Butler KM, Cahill I, McMorrow J, Philbin M, et al. Antenatal hepatitis B screening - is there a need for a national policy? Ir Med J. 2001 Apr;94(4):111-2, 114.

31. Karatapanis S, Skorda L, Marinopoulos S, Papastergiou V, Drogosi M, Lisgos P, et al. Higher rates of chronic hepatitis B infection and low vaccination-induced protection rates among parturients escaping HBsAg prenatal testing in Greece: a 2-year prospective study. Eur J Gastroenterol Hepatol. 2012 Aug;24(8):878-83.

32. Rimseliene G, Nilsen O, Klovstad H, Blystad H, Aavitsland P. Epidemiology of acute and chronic hepatitis B virus infection in Norway, 1992–2009. BMC Infect Dis. 2011;11:153.

33. van Steenbergen JE, Leentvaar-Kuijpers A, Baayen D, Dukers HT, van Doornum GJ, van den Hoek JA, et al. Evaluation of the hepatitis B antenatal screening and neonatal immunization program in Amsterdam, 1993-1998. Vaccine. 2001 Oct 12;20(1-2):7-11.

34. van Steenbergen JE, Baayen D, Peerbooms PG, Coutinho RA, Van Den Hoek A. Much gained by integrating contact tracing and vaccination in the hepatitis B antenatal screening program in Amsterdam, 1992-1999. J Hepatol. 2004 Jun;40(6):979-85.

35. Jordan R, Law M. An appraisal of the efficacy and cost effectiveness of antenatal screening for hepatitis B. J Med Screen. 1997;4(3):117-27.

36. Dwyer MJ, McIntyre PG. Ante-natal screening for hepatitis B surface antigen: an appraisal of its value in a low prevalence area. Epidemiol Infect. 1996 Aug;117(1):121-31.

37. Tormans G, Van Damme P, Carrin G, Clara R, Eylenbosch W. Cost-effectiveness analysis of prenatal screening and vaccination against hepatitis B virus--the case of Belgium. Soc Sci Med. 1993 Jul;37(2):173-81.

38. Doroshenko A, Sherrard J, Pollard AJ. Syphilis in pregnancy and the neonatal period. Int J STD AIDS. 2006 Apr;17(4):221-7; quiz 228.

39. Carey JC. Congenital syphilis in the 21st century. Curr Womens Health Rep. 2003 Aug;3(4):299-302.

40. Kiss H, Widhalm A, Geusau A, Husslein P. Universal antenatal screening for syphilis: is it still justified economically? A 10-year retrospective analysis. Eur J Obstet Gynecol Reprod Biol. 2004 Jan 15;112(1):24-8.

41. Hawkes S, Matin N, Broutet N, Low N. Effectiveness of interventions to improve screening for syphilis in pregnancy: a systematic review and meta-analysis. Lancet Infect Dis. 2011 Sep;11(9):684-91.

42. Meyer Sauteur PM, Truck J, Bosshard PP, Tomaske M, Moran Cadenas F, Lautenschlager S, et al. Congenital syphilis in Switzerland: gone, forgotten, on the return. Swiss Med Wkly. 2012 Jan 11;141:w13325.

43. Newman L, Kamb M, Hawkes S, Gomez G, Say L, Seuc A, et al. Global estimates of syphilis in pregnancy and associated adverse outcomes: analysis of multinational antenatal surveillance data. PLoS Med. 2013;10(2):e1001396.

44. Tridapalli E, Capretti MG, Reggiani ML, Stronati M, Faldella G; Italian Neonatal Task Force of Congenital Syphilis for the Italian Society of Neonatology – Collaborative Group. Congenital syphilis in Italy: a multicentre study. Arch Dis Child Fetal Neonatal Ed. 2012 May;97(3):F211-3.

45. Connor N, Roberts J, Nicoll A. Strategic options for antenatal screening for syphilis in the United Kingdom: a cost effectiveness analysis. J Med Screen. 2000;7(1):7-13.

46. Low N, Hawkes SJ. Putting the magic in magic bullets: top three global priorities for sexually transmitted infection control. Sex Transm Infect. 2011;87:44-6.

47. Stray-Pedersen B. Economic evaluation of maternal screening to prevent congenital syphilis. Sexually transmitted diseases. Sex Transm Dis. 1983 Oct-Dec;10(4):167-72.

48. Kahn JG, Jiwani A, Gomez GB, Hawkes SJ, Chesson HW, Broutet N, et al. The cost and cost-effectiveness of scaling up screening and treatment of syphilis in pregnancy: a model. PloS one. 2014;9(1):e87510.

49. Lugner AK, Mollema L, Ruijs WL, Hahne SJ. A cost-utility analysis of antenatal screening to prevent congenital rubella syndrome. Epidemiol Infect. 2010 Aug;138(8):1172-84.

50. Anderson SR, Righarts A, Maguire H. Surveillance of antenatal infections – HIV, hepatitis B, syphilis and rubella susceptibility in London. Commun Dis Public Health. 2004 Dec;7(4):251-7.

51. Byrne L, Brant L, Reynolds C, Ramsay M. Seroprevalence of low rubella IgG antibody levels among antenatal women in England tested by NHS Blood and Transplant: 2004-2009. Is rubella susceptibility increasing? Vaccine. 2012 Jan 5;30(2):161-7.

52. Matthews LA, Lawrance LM, Gray D, Gray S. An audit of rubella IgG antibody status in antenatal women in a NHS Trust over 5 years (2005-2009). Epidemiol Infect. 2011 Nov;139(11):1720-6.

53. O'Dwyer V, Bonham S, Mulligan A, O'Connor C, Farah N, Kennelly MM, et al. Antenatal rubella immunity in Ireland. Ir Med J. 2013 Sep;106(8):232-5.

54. Gyorkos TW, Tannenbaum TN, Abrahamowicz M, Delage G, Carsley J, Marchand S. Evaluation of rubella screening in pregnant women. CMAJ. 1998 Nov 3;159(9):1091-7.

55. Buffolano W, Agnese M, Pizzuti R. Secular trend on congenital infections: insights from Campania region register for perinatal infection, southern Italy. J Matern Fetal Neonatal Med. 2011 Oct;24 Suppl 1:94-6.

56. Calimeri S, Capua A, La Fauci V, Squeri R, Grillo OC, Lo Giudice D. Prevalence of serum anti-rubella virus antibodies among pregnant women in southern Italy. Int J Gynaecol Obstet. 2012 Mar;116(3):211-3.

Appendix 1. Literature search on the topic of cost-effectiveness of antenatal screening

Centre for Reviews and Disseminations

1	syphilis.sh.	72	
2	HIV infections.sh.	4759	
3	hepatitis B.sh.	977	
4	rubella.sh.	87	
5	(rubella* or "three day measles" or "german measles").ti,ab,kw.	280	A
6	("HTLV III LAV Infections" or "HTLV III Infections").ti,ab,kw.	0	
7	1 or 2 or 3 or 4 or 5 or 6	6041	
8	mass screening.sh.	3382	
9	neonatal screening.sh.	207	
10	prenatal diagnosis.sh.	256	
11	8 or 9 or 10	3766	
12	pregnancy.sh.	14270	
13	pregnancy complications.sh.	826	
14	12 or 13	14284	
15	7 and 11 and 14	43	
16	(prenatal or pre-natal or antenatal or ante-natal or pregnan* NEAR2 screen*).af.	4106	
17	7 and 16	141	
18	15 or 17	149	
19	economics.af.	2958	
20	exp "costs and cost analysis"/.sh.	18256	
21	economics, dental/	3	
22	exp "economics, hospital"/	1384	
23	economics, medical/	32	
24	economics, nursing/	14	
25	economics, pharmaceutical/	211	
26	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	31504	
27	(expenditure$ not energy).ti,ab.	585	
28	value for money.ti,ab.	57	A
29	budget$.ti,ab.	271	
30	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29		
31	((energy or oxygen) adj cost).ti,ab.	220	
32	(metabolic adj cost).ti,ab.	49	
33	((energy or oxygen) adj expenditure).ti,ab.	1519	
34	31 or 32 or 33	1714	
35	30 not 34	36090	
36	letter.pt.	5231	
37	editorial.pt.	301	
38	historical article.pt.	69	
39	36 or 37 or 38	5597	
40	35 not 39	36020	
41	Animals/	6983	
42	Humans/	407047	
43	41 and 42	6978	
44	41 not 43	5	
45	40 not 44	36016	
46	18 and 45	63	

Ovid MEDLINE
Ovid MEDLINE Daily Update

1	exp Syphilis/	21555
2	exp HIV Infections/	215924
3	exp Hepatitis B/	43196
4	exp Rubella/	7185
5	(rubella* or "three day measles" or "german measles").ti,ab.	9912
6	("HTLV III LAV Infections" or "HTLV III Infections").ti,ab.	29
7	1 or 2 or 3 or 4 or 5 or 6	285293
8	exp Mass Screening/	93878
9	exp Prenatal Diagnosis/	57125
10	exp Neonatal Screening/	6582
11	8 or 9 or 10	148860
12	exp Pregnancy/	680883
13	exp Pregnancy Complications/	322016
14	12 or 13	713713
15	7 and 11 and 14	1698
16	((prenatal or pre-natal or antenatal or ante-natal or pregnan*) adj2 (diagnos* or screen*)).ti,ab.	28314
17	7 and 16	965
18	15 or 17	2149
19	(news or comment or letter or editorial or interview).pt.	1319199
20	18 not 19	1882
21	exp Economics/	467445
22	quality-adjusted life years/	6054
23	exp models, economic/	9182
24	Markov Chains/	8614
25	Monte Carlo Method/	18018
26	Decision Trees/	8285
27	economic$.ti,ab.	127038
28	(cost? or costing? or Costly or costed).ti,ab.	277671
29	(price? or pricing?).ti,ab.	20775
30	(pharmacoeconomic? or (pharmaco? adj economic?)).ti,ab.	2995

31	budget$.ti,ab.	15968
32	expenditures$.ti,ab.	9259
33	(value adj1 (money or monetary)).ti,ab.	299
34	(fee or fees).ti,ab.	10796
35	"health related quality of life".ti,ab.	17361
36	hrqol.ti,ab.	5607
37	"quality adjusted life year$".ti,ab.	4682
38	qaly$.ti,ab.	4047
39	cba.ti,ab.	8429
40	cea.ti,ab.	15063
41	cua.ti,ab.	
42	(cost adj utilit$).ti,ab.	1980
43	markov$.ti,ab.	10004
44	"monte carlo".ti,ab.	18537
45	(decision adj2 (tree$ or analy$ or model)).ti,ab.	9484
46	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45	810427
47	(news or comment or letter or editorial or interview).pt.	1319199
48	46 not 47	733807
49	20 and 48	279
50	limit 49 to yr="1990 -Current"	239

Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE

1	((prenatal or pre-natal or antenatal or ante-natal or pregnan*) adj2 (diagnos* or screen*)).ti,ab,kw.	30224
2	(syphilis or hiv* or "hepatitis b" or "german measles" or "three day measles" or rubella or "HTLV III LAV Infections" or "HTLV III Infections").ti,ab,kw.	286109
3	1 and 2	1111
4	(cost–benefit or cost-effective* or econom* or qaly).ti,ab,kw.	229506
5	3 and 4	124

NLM PubMed (epubs ahead of print)

#7	(#5) AND #6	8
#6	(qaly or qalys or economic or cost–benefit or cost-effective*)	686808
#5	(#4) AND #3	32
#4	pubstatusaheadofprint	154787
#3	(#1) AND #2	11449
#2	(syphilis or hiv or "hepatitis b" or rubella* or "german measles" or "three day measles" or "HTLV III LAV Infections" or "HTLV III Infections")	354311
#1	((prenatal or pre-natal or antenatal or ante-natal or neonatal or pregnan*) and (diagnosis or screen*)	421869

Appendix 2. Literature search on the topic of effectiveness of antenatal screening

1.	exp Rubella/	7306
2.	exp Syphilis/	22141
3.	exp HIV Infections/	228801
4.	exp Hepatitis B/	45197
5.	exp Mass Screening/	98703
6.	exp Prenatal Diagnosis/	59184
7.	exp Neonatal Screening/ 7028	
8.	5 or 6 or 7	155662
9.	exp Pregnancy/	702836
10.	exp Pregnancy Complications/ 333484	
11.	9 or 10	736539
12.	1 and 8 and 11	201
13.	2 and 8 and 11	274
14.	3 and 8 and 11	1084
15.	4 and 8 and 11	268
16.	((prenatal or pre-natal or antenatal or ante-natal or pregnan*) adj2 (diagnos* or screen*)).ti,ab. 29450	
17.	1 and 16	115
18.	2 and 16	208
19.	3 and 16	491
20.	4 and 16	222
21.	12 or 17	246
22.	13 or 18	372
23.	14 or 19	1325
24.	15 or 20	374
25.	exp European Union/ 11542	
26.	exp Finland/	27409
27.	exp Sweden/	56357
28.	exp Norway/	29293
29.	exp Denmark/	36465
30.	exp Germany/	123683
31.	exp Austria/	15351
32.	exp Estonia/	1781
33.	exp Lithuania/	2039
34.	exp Latvia/	966
35.	exp Poland/	37190
36.	exp Hungary/	15501
37.	exp Romania/	7913
38.	exp Bulgaria/	5828
39.	exp Greece/	13530
40.	exp Malta/	525
41.	exp Italy/	68354
42.	exp Spain/	52363
43.	exp France/	76523
44.	exp Great Britain/	297274
45.	exp Czech Republic/	4757
46.	exp Slovakia/	1714
47.	exp Switzerland/	27770
48.	exp Liechtenstein/	27
49.	exp New Zealand/	28702
50.	exp Australia/	97387
51.	exp United States/	1087112
52.	exp Canada/	118200
53.	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52	2149316
54.	exp Netherlands/	48494
55.	exp Belgium/	13605
56.	53 or 54 or 55	2204280
57.	21 and 56	66
58.	22 and 56	105
59.	23 and 56	591
60.	24 and 56	173
61.	limit 59 to yr="2000 -Current"	263 (HIV)

Without restriction to country:

62.	limit 12 to yr="2000 -Current"	51	(Rubella)
63.	limit 13 to yr="2000 -Current"	151	(Syphilis)
64.	limit 15 to yr="2000 -Current"	99	(HepB)

European Centre for Disease Prevention and Control (ECDC)

Postal address:
Granits väg 8, SE-171 65 Solna, Sweden

Visiting address:
Tomtebodavägen 11A, SE-171 65 Solna, Sweden

Tel. +46 858601000
Fax +46 858601001
www.ecdc.europa.eu

An agency of the European Union
www.europa.eu

Subscribe to our monthly email
www.ecdc.europa.eu/en/publications

Contact us
publications@ecdc.europa.eu

Follow us on Twitter
@ECDC_EU

Like our Facebook page
www.facebook.com/ECDC.EU

ECDC is committed to ensuring the transparency and independence of its work

In accordance with the Staff Regulations for Officials and Conditions of Employment of Other Servants of the European Union and the ECDC Independence Policy, ECDC staff members shall not, in the performance of their duties, deal with a matter in which, directly or indirectly, they have any personal interest such as to impair their independence. Declarations of interest must be received from any prospective contractor(s) before any contract can be awarded.
www.ecdc.europa.eu/en/aboutus/transparency

HOW TO OBTAIN EU PUBLICATIONS

Free publications:

- one copy:
  via EU Bookshop (http://bookshop.europa.eu);
- more than one copy or posters/maps:
  from the European Union's representations (http://ec.europa.eu/represent_en.htm);
  from the delegations in non-EU countries (http://eeas.europa.eu/delegations/index_en.htm);
  by contacting the Europe Direct service (http://europa.eu/europedirect/index_en.htm) or
  calling 00 800 6 7 8 9 10 11 (freephone number from anywhere in the EU) (*).

  (*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

Priced publications:

- via EU Bookshop (http://bookshop.europa.eu).

Publications Office