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Accepted author version posted online: 21 Jul 2016.
Published online: 21 Jul 2016.

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1

ABSTRACT

Introduction: Congenital and perinatal infections are a leading cause of neonatal and infant morbidity and mortality. Maternal screening, vaccines or treatment where available, constitute effective prevention strategies to reduce the burden of these diseases. Data on the burden of congenital and perinatal infections are very limited for low and middle-income regions.

Areas covered: This review aims to summarize the burden of congenital and perinatal infections and the main challenges for their control in resource-limited settings. Articles were identified through the main electronic databases and cover the period 1971- 2016.

Expert commentary: Estimates from low and middle-income countries indicate that the burden of congenital infections may be higher in these regions than in industrialized countries. As preventive and curative strategies are available to tackle some of these infections, efforts at the international and national levels must be made to implement those and thus reduce their burden in resource-limited countries.

1.- BACKGROUND

Foetal, perinatal and childhood morbidity and mortality are significantly influenced by infections acquired *in utero* or in the immediate post-natal period. These infections may be mild or subclinical for the mother, but if they are vertically transmitted can result in devastating consequences for the newborn[1,2]. Transmission of the pathogens may occur prenatally (through transplacental passage of organisms), perinatally (direct contact with blood and maternal secretions or by ascending route from the birth channel), and postnatally (from exposure to infected breast milk while breastfeeding)[2]. Infections acquired *in utero* are categorized under "congenital" infections, whereas those acquired around the time of delivery and the immediate postpartum period are called "perinatal" infections[1].

Congenital and perinatal infections are well-described causes of perinatal morbidity and stillbirths. The acronym "TORCH" was introduced by Nahmias in 1971 to underline a group of pathogens that cause congenital and perinatal infections: **T**oxoplasma gondii *(T. gondii)*; **R**ubella virus; **C**ytomegalovirus (CMV) and **H**erpes simplex virus (HSV)[3]. The diagnostic problems encountered in the evaluation of a suspected perinatal infection and the complexities of the evaluation process for the original four TORCH agents, made it necessary to expand the original TORCH complex and include new agents[4]. Currently, TORCH stands for the following: **T**. gondii;   **O**ther: syphilis, hepatitis B virus (HBV), hepatitis C virus (HCV), varicella zoster virus (VZV), human immunodeficiency virus (HIV), parvovirus B19 (B19V), enteroviruses, lymphocytic choriomeningitic virus, , tuberculosis, listeriosis and other less recognized pathogens such as Chlamydia trachomatis and Ureaplasma urealyticum; **R**ubella virus; **C**MV and **H**SV[2,5,6]. A further expansion of this

2

acronym, CHEAPTORCHES, was proposed by Ford-Jones and Kellner in 1995 but it is not widely used.[7]. It includes: **C – C**hickenpox and shingles; **H – H**epatitis B, C, (D), E; **E – E**nterovirus; **A – A**IDS (HIV infection); **P – P**arvovirus B19 ;**T – T**oxoplasmosis; **O – O**ther (Group B Streptococcus, Listeria, Candida, Lyme disease); **R – R**ubella; **C – C**ytomegalovirus; **H – H**erpes simplex; **E – E**verything else sexually transmitted (Gonorrhea, Chlamydia infection, Ureaplasma urealyticum, Human papillomavirus); **S – S**yphilis.

Although there are no specific estimates regarding the global burden of congenital and perinatal infections and their impact on disability and/or neonatal cause-of-death, they may contribute to death due to prematurity and low birth weight (35.7% of neonatal cause-of-death[8]), neonatal infections and congenital abnormalities (15.6% and 10.5% respectively)[8]. A study conducted in the UK over a 21 years-period demonstrated that viruses contributed to 4.2% of stillbirths and 13.2 of infant deaths, confirming parvovirus and CMV, vertically transmitted, as the commonest viruses associated to stillbirth and neonatal deaths[9]. Producing global estimates of the attributable stillbirth, neonatal births or disability due to congenital infections in low-income countries appears challenging, primarily because of the scarcity of prevalence or risk data. In those settings, it would seem reasonable to assume a higher burden of congenital infections, partly may be assumed because of the higher underlying prevalence of HIV (frequently associated to CMV[10], HSV[11] and hepatitis B[12] vertical transmission); but also in relation to the challenges in the implementation of effective vaccines, such as for instance the anti-rubella vaccine. The presence of infections that may not be endemic in more industrialized parts of the world may also play a role. For instance, in sub-Saharan Africa, malaria is estimated to cause ~20% of stillbirths (global estimate 8.2%) and HIV could account for about 0.7% in this region. Similarly, maternal syphilis may be responsible for 7.7% of stillbirths worldwide and 11.2% in sub-Saharan Africa[13]. So, a first step to prevent these foetal deaths should be to improve prevention and treatment of malaria, syphilis and HIV.

Some experts consider the acronym TORCH out-dated[5], largely due to the growing number of infections listed under the "other" category. However, the use of this acronym reminds clinicians that several infectious agents can produce similar and potentially devastating effects on the foetus and the nervous system in development.

The manifestations of congenital infections depend on several independent factors such as the effect of the pathogen on organogenesis, the timing of infection with respect to gestational age (GA), the presence or absence of maternal immunity, the immaturity of the foetal immune response and the mode of acquisition and load of the infection[14]. While each of the congenital and perinatal infections can cause distinct clinical manifestations and *sequelae*, some of these infections share characteristics (Table 1).

3

For many of these pathogens, prenatal screening is available and treating the infected pregnant women appears as an effective measure to prevent vertical transmission to their offspring. Early recognition of congenital disease in newborns is key and treatment and/or prevention strategies are internationally recognized and available, although not necessarily implemented in low and middle-income countries (LMIC) (Table 2).

This review aims to summarize the burden of congenital and perinatal infections and the main challenges for their control in resource-limited settings. It includes congenital infections that are present at the time of delivery as well as perinatally-acquired ones transmitted during or immediately after delivery. Although HIV can also be vertically transmitted, we will only describe it briefly, focused in the context of its impact on the control of other pathogen's transmission, since, due to its burden and impact, congenital HIV deserves a separated review. Assuming a higher burden of congenital infections in LMIC, we aim to highlight key aspects of their epidemiology, diagnosis, management and prevention in resource-limited countries.

We have included data on incidence for those infections when available, but this review has not been designed to estimate absolute risk, since data have not been abstracted in a systematic manner.

2.- SEARCH METHODOLOGY

Articles were identified through electronic searches of Pubmed, Health InterNetwork Access to Research Initiative (HINARI) and The Cochrane Library without any language or date restrictions, covering a period of 45 years (from 1971 to 2016). Pubmed was searched through the use of a broad sensitive filter using the following combination of search terms: "congenital", "infection", "developing" and "countries", "low-income" and "countries" and "lower-middle income" and "countries" yielding 353 results, while the same search found out 20789 results when the terms "developing" and "countries", "lower-middle-income" and "countries" and "low-income" and "countries" were dropped. Limits were applied to exclude studies on animals. The references of the retrieved papers were further hand-searched for additional studies. Unpublished and/or grey literature was not reviewed. Diseases of interest for this article were restricted to congenital infections belonging to the TORCH complex. Searching specific congenital infections, "congenital" and "toxoplasmosis" were used as search terms for congenital toxoplasmosis, yielding 3466 articles; "congenital" and "rubella" 3217 results, "congenital", "cytomegalovirus" and "infection", provided 2917 results; and "congenital" "herpes simplex" and "infection", 637. Search of others congenital infections as syphilis was performed using search terms "congenital" and "syphilis", yielding 3346 results, varicella congenital infection using "congenital", "varicella" and "syndrome", yielding 194 articles, "congenital" and

4

"hepatitis b" 455 results, "congenital" parvovirus B19" yielding 211 and other infections vertically transmitted (hepatitis c, zika virus, dengue and chagas) yielded 1100 articles. Our outcomes of interest were related to the epidemiology and challenges in diagnosis and treatment of congenital infections, focussing on lower-middle and low-income countries rather than more industrialized ones. We used the concept "resource-constrained environment" defined as the setting in which production activities cannot exceed the volume of available resources. These constraints may be of a physical or technical nature [15]. A total of 170 articles were finally included in this review (Figure 1).

3.- BURDEN OF CONGENITAL AND PERINATAL INFECTIONS IN LOWER-MIDDLE AND LOW-INCOME COUNTRIES

3.1 CONGENITAL TOXOPLASMOSIS

Toxoplasmosis infection is usually asymptomatic in humans, however, foetal infection can result in severe disease causing congenital toxoplasmosis (CT). The global estimated incidence of CT is 190 100 annual cases (95% CI: 179,300 – 206,300), approximately 1.5 cases of CT per 1000 live births [16]. Seroprevalence for toxoplasma among pregnant women varies among countries. The highest prevalence is noted in regions with tropical climates, where the toxoplasma oocysts can survive in soil, as well as countries with dietary customs of raw or unprocessed meat[5]. Circa 50-80% of women of child-bearing age in Brazil have antibodies to *T. gondii*[17], 44% in France [18] or 9.1% in the USA[19].

Regarding the annual incidence, the global burden of CT was estimated to be 9.6 Disability-adjusted life years (DALYs) (95% CI: 5.8–15) per 1000 live births[16]. However, there are important differences among regions, peaking at 19 DALYs (95% CI: 13–22) per 1000 live births, in South America, 17 DALYs (95% CI: 8.5–26) in Eastern Mediterranean region and 15 DALYs (95% CI: 8.3–24) in some low-income African countries compared with only 2.8 DALYs (95% CI: 1.3–4.3) per 1000 live births in some European countries[16]. Although evidence suggests seroprevalence is decreasing in high-income countries[16], regions where a rapid process of industrialization is occurring and where meat consumption is growing, could witness an increase of the risk of exposure to *T.gondii*.

South America is suffering the highest burden of CT. Both, incidence and frequency of *sequelae* secondary to CT are higher in this region[20]. Three genotypes of *T.gondii* have been isolated. Genotype 2 is predominant in Europe while non-type-2 genotypes, which are common in America, appear to associate more frequent and more severe sequelae[16].

3.2 CONGENITAL RUBELLA SYNDROME

Rubella remains an important pathogen worldwide, with roughly 100,000 cases of Congenital Rubella Syndrome (CRS) estimated to occur every year[21]. The highest risk of CRS is found in countries with high rates of susceptibility to rubella among women of childbearing age[22,23]. The incidence of CRS in developing countries was reported as 0.6–2.2 per 1000 live births which is not far from the rates reported in Western countries in the pre-vaccine era[23]. Since the introduction of the vaccine, congenital rubella cases reported have decreased drastically. Nevertheless estimates suggest that the burden of CRS in regions that have not yet introduced rubella-containing vaccine could be very high, although CRS are substantially under-reported[24]. The number of member states reporting CRS cases increased from 75 in 2000 to 129 in 2012[24]. In 2012, substantially more cases were reported in Europe (30,536 cases) and Western Pacific region (44,275 cases) than in other regions (19,219 cases)[24].

3.3 CONGENITAL CMV INFECTION

Congenital CMV infection is the most prevalent congenital infection worldwide, although it remains a neglected public health problem. Although the global prevalence of congenital CMV infection has been reported to vary from approximately 0.2% to 2% (mean 0.65%)[25,26], most of these studies have been conducted in high-income regions of Europe, USA or Japan. Data from low-income countries varies substantially, with some reported prevalence as high as 6–14%[10,27,28]. Higher overall rates are found in countries with higher maternal CMV seroprevalence[25,26,29]. Those rates lead in seropositive hosts to an increased chance of reactivation or reinfection. Furthermore, seronegative hosts within the general population are at greater risk for primary infection.

Most congenital CMV cases in developing countries result from women with preexisting antibodies, a transmission mechanism more poorly understood as a cause of congenital CMV disease. Emerging data from populations with very high seroprevalence, usually from LMIC countries, suggest that prevalence and incidence of congenital CMV infection is higher than in developed countries. Consequently, congenital CMV infection could be an important cause of hearing loss (on the associated consequences of this infection) in resource-limited settings[30,31]. Studies that accurately estimate disability, mortality burden and how it may be affected by other prevalent conditions such as HIV infection, malnutrition or malaria in resource-constrained settings are scarce. Children born to mothers co-infected with HIV type 1 present higher prevalence of congenital CMV infection than those born to HIV-negative mothers, increasing from 2.3% to 10.3% [32-36]. Studies in industrialized countries support an increased risk for congenital CMV infection in neonates born to HIV/CMV co-infected mothers [32,33] and CMV may act as a cofactor for HIV disease progression in HIV/CMV co-infected newborns[37]. In addition, among HIV-infected children seems to be an impairment of the immunological response to CMV infection with a delay in the clearance of CMV viremia

6

and high CMV peak loads. Apparently, the relationship between HIV and CMV is bidirectional[38]. In sub-Saharan Africa, the burden of HIV-1 in women of reproductive age is alarming, reaching 40% in some regions[39] and MTCT risks may range from 25.8% (no antenatal ARVs) to 10.9% (Options B/B+)[40]. However, the prevalence of CMV infection has decreased over time among neonates exposed but not infected with HIV-1. This prevalence has reached levels similar to those observed in the general population, following the introduction and increasing use of highly active antiretroviral therapy (HAART) for prevention of mother-to-child transmission (MTCT) of HIV[33,41].

Unfortunately, maternal and birth CMV prevalence and long-term follow-up data for congenitally infected children for many parts of the world are scarce, likely underestimating the global impact of congenital CMV infection.

3.4 NEONATAL HERPES

Neonatal herpes is usually the result of HSV-2 infection, which is the primary type of HSV associated with genital infection, although recent studies indicate that HSV-1 may also play a major role in causation[42]. HSV-2 is a major global health concern, with a number of negative health impacts. The overall prevalence of HSV-2 remains high worldwide although varies by country [43]. Following primary infection both types of herpes establish lifelong latent infections, which periodically reactivate and may be associated with recurrent episodes of disease. Approximately 20% of pregnant women are infected genitally with HSV-2, and most of them are unaware of this[44]. It is estimated that one neonate in 3200 live births has HSV-2 infection[45], and without treatment, 80% of infants with disseminated disease die and those who do survive are often severely brain damaged[46],[47]. In addition to being the main cause of genital ulcer disease, HSV-2 is a major cofactor fuelling the HIV epidemic, mainly in sub-Saharan Africa and may account for 40–60% of new HIV infections in high HSV-2 prevalence populations[48]. Sero-epidemiological studies of HSV-2 show that prevalence of HSV-2 is at least two fold higher in sub-Saharan Africa (40% of Tanzanian women infected with HSV-2[49]) than in the USA or Europe[50,51]. As a result, MTCT of both pathogens can be significantly increased[52,53], being a preventable cause of neonatal morbidity and mortality.

3.5 CONGENITAL SYPHILIS

Congenital syphilis (CS) occurs after infection of the placenta in pregnant women who have a primary or secondary syphilis infection. In 2008, the WHO estimated that, worldwide, approximately 1.4 million pregnant women had "probable active syphilis" (PAS) or syphilis infections sufficiently active to result in MTCT[54]. Several models have been proposed to estimate a prevalence of 75% (range: 50-80%)[55] of adverse pregnancy outcomes in untreated maternal syphilis. Such maternal infections would cause globally an estimated 521,000 – 1,575,000 new CS cases, and approximately 521,000 adverse perinatal outcomes,

7

characterized as 212,000 stillbirths, 92,000 neonatal deaths, 65,000 preterm or low birth weight infants, and 152,000 syphilis-infected newborns[55-58]. The proportion of pregnant women globally receiving adequate testing and treatment for syphilis is currently unknown. WHO is monitoring syphilis testing and treatment coverage through the HIV Universal Access reporting system, but quality data are not yet available from all countries[54]. Sixty-three of 149 LMIC reported on coverage of syphilis testing during antenatal care (ANC) in 2011, with a median of 68% of women in the reporting countries being tested for syphilis at their first ANC visit[59]. Seroprevalence during pregnancy is generally low in Europe (0.02%) and US (4.5%) but may increase up to 18% in Sub-Saharian Africa[59].

Overall estimates suggest that untreated maternal syphilis may result in approximately 304,091 foetal or perinatal deaths and 216,814 syphilis-infected infants at risk for early death[54]. Regarding adverse outcome by region, most of adverse outcomes (87%) would be in Africa and Asia. CS also remains an important cause of severe psychomotor disability and death in infants, especially in resource poor settings. Case fatality rates (CFR) of 15% in Africa and 6.4% in US have been reported[59].

3.6 CONGENITAL VARICELA SYNDROME

Maternal chickenpox in the first 20 weeks of pregnancy is associated with an incidence of congenital varicella syndrome (CVS) of 0.91%, although this incidence could increase among pregnant women from tropical countries where the seroprevalence in adulthood is lower[60]. Few congenital infections have been reported, possibly because most women of childbearing age are immune in developed countries and cases from developing countries remain severely underreported. No data have been found related to prevalence of CVS in developing countries. It is known that in temperate climes, this percentage is lower[61]. Several studies performed in UK among South Asian migrant women and British women showed lower seroprevalence of VVZ in migrant women born in South Asia[61,62]. These women have a higher risk of VZV infection during pregnancy if they migrate to settings with higher prevalence of VVZ and this infection could produce CVS or perinatal chickenpox[62].

3.7 HEPATITIS B INFECTION

HBV is the most serious type of viral hepatitis causing a potentially life-threatening liver infection and eventually leading to chronic liver disease and liver cancer[63]. Perinatal HBV infection occurs in ~ 1% of infants and is strongly associated with Hepatitis B e antigen (HBeAg) positivity among childbearing women[64]. Babies born to HBeAg positive mothers have the highest risk of developing chronic HBV infection (CHB) and becoming chronic HBV carriers[65]. Overall prevalence of HBeAg in childbearing women reaches to 20-50% in some regions. HBV co-infection among HIV positive pregnant women is a recognized public health issue, increasing mortality and morbidity in this population[66].

8

There are 387 million chronic carriers of HBV worldwide[67]. A recent systematic review has shown that the prevalence of chronic HBV infection worldwide is 3.61%, being the highest endemicity in countries of the African region (8.83%,) and Western Pacific region (5.26%)[68], whereas less than 1% of the population in Western Europe and North America is chronically infected[63,67,68]. This prevalence has clearly declined in many countries after the implementation of routine infant immunization programs and the achievement of high coverage[69]. However, despite improvements, chronic HBV infection remains highly prevalent in some countries in Africa (South Sudan, 22.38%); or in the Pacific (Kiribati 22.70% and Papua New Guinea 14.59%)[68]. Perinatal transmission occurs regionally in different magnitudes. The risk of perinatal transmission is lower in Africa than in Asia, a disparity that could be due to a lower prevalence of hepatitis B e antigen (HBeAg) and other differences in the pathogenic characteristics of circulating HBV genotypes[12]. A study performed in Libya showed HBsAg positivity in 1.5% and maternal to child transmission in 60.9% of the cases[70] while in Ghana, with higher prevalence (16%) the transmission to neonates occurred only in 8.4%[71]. However, in HIV endemic settings, HBV prevalence and mother to child transmission may be increased. Perinatal HBV infection is associated with a 90% risk of CHB as compared with a risk of less than 5% among adults with intact immunity. CHB accounts for an estimated 21% of HBV related deaths, ranging from 13% in the Eastern Mediterranean region to 26% in the Western Pacific region[72].

3.8 HEPATITIS C INFECTION

It has been estimated that the global prevalence of hepatitis C infection varies between 2-3% and that around 120–200 million people live with chronic hepatitis C infection worldwide[73]. The prevalence of that infection varies considerably by country and region, and the true burden of disease is not well established in many countries. The highest prevalence of HCV appears to be in Sub-Saharan Africa (5.3%), followed by the Eastern Mediterranean (4.6%), Western Pacific (3.9%) and South-Eastern Asia (2.15%) regions. Europe and United States have the lowest prevalence of HCV (1.03% and 1.6% respectively)[74]. HIV co-infection accelerates the progression of HCV and represents a major public health challenge. Estimates of HCV prevalence among HIV infected persons range from 5 to 33%[73]. A global systematic review of Hepatitis C seroprevalence and HIV co-infection estimated a seroprevalence of 4% among pregnant women[75]. Presence of maternal HCV viremia is a critical factor in MTCT of HCV, and maternal HIV co-infection is an important risk factor[76]. A recent meta-analysis estimated the pooled risk of HCV vertical transmission from HCV antibody and HCV RNA–positive women who were HIV negative at 5.8% as opposed to a 10.8% risk of HCV vertical transmission in children born to HIV-positive women. However, the risk to children born to HCV antibody–positive, RNA-negative mothers was negligible[76]. The natural history and histopathology of HCV-related liver disease in children are still conflicting and variable but generally not as severe as in adults[77].

3.9 CONGENITAL PARVOVIRUS B19 INFECTION

Parvovirus B19 infection is common in childhood, with serologic evidence of previous infection seen in about approximately 35% to 53% of pregnant women, offering, in these cases, no risk to the foetus. The incidence of B19V infection in pregnancy has been estimated at 3.3%- 3.8%[78]. No available data of congenital parvovirus B19 infection in developing countries have been found as part of this review.

3.10 HIV INFECTION

In 2014, 36.9 million people were living with HIV. Although globally, the incidence of HIV is decreasing, the total number of people living with HIV continues to increase, in large part because more people globally are accessing antiretroviral therapy and as a result are living longer, healthier lives. New HIV infections have fallen by 35% since 2000 (by 58% among children) and AIDS-related deaths have fallen by 42% since the peak in 2004[79].

The region more affected is Sub-Saharan Africa, where 1.4 million people were newly infected out of a total of 2 million new HIV infections in 2014 globally, mainly HIV-1 infections. However, the incidence in this region has decreased by 41% since 2000. In Europe and USA, the number of new infections has remained fairly stable since 2000 and in regions as Eastern Europe and central Asia and Middle East and North Africa, new infections rose by 30% between 2000 and 2014[79].

Globally, 3.2 million children under 15 were living with HIV in 2013, comprising 9.1% of all people living with HIV. Most of the children HIV-infected acquired the infection from their mothers. In 2013, an estimated 1.5 million women living with HIV gave birth, a figure virtually unchanged from those in 2009[80].

Of the 3.2 million children living with HIV, 91% live in sub-Saharan Africa, 6% live in Asia and the Pacific and the remaining 3% are situated in the rest of the world[80]. Globally, HIV causes 63.8 per 1000 deaths in children aged 1-59 months[81].

3.11 OTHER CONGENITAL INFECTIONS, EMERGING OR NEGLECTED

3.11.1 Congenital Chagas disease

Congenital Chagas disease is a neglected disease. The global epidemiologic profile of Chagas disease (CD) is the result of domestic vector borne transmission mainly in Latin America and large-scale rural-to-urban migration over the past 50 years[82].

The estimated global prevalence of *T. cruzi* infection declined from 18 million in 1991, when the first regional control initiative began, to 5.7 million in 2010[83,84]. CD has been estimated to cause more than 10,000

deaths annually and 30-40% of people either have or will develop cardiomyopathy, digestive mega syndromes, or both[84,85].

At least two million childbearing women are estimated to be chronically infected with *Trypanosoma cruzi* in Latin America with the incidence of congenital infection being at least 15,000 cases/year[86]. Vertical transmission may be repeated in each pregnancy (family clustering of congenital cases) and can occur from one generation to another (vertical transmission).

Materno-foetal transmission rates range from 0 to 5.2%[87]. Higher prevalence of MTCT of Chagas diseases are found in Brazil, Paraguay, Bolivia and Argentina[87]. Outside endemic areas, Chagas disease often is unrecognized because pregnant women may be asymptomatic. As a consequence of migration of infected women, mainly from Bolivia, congenital transmission has also been recorded from non-endemic countries. A systematic review found that in several studies conducted in Spain, 4.3% of children born to infected mothers were infected[87]. Associated symptoms in the infant include prematurity/low birth weight, respiratory distress syndrome, hepato and splenomegaly, and neurologic signs[87].

3.11.2 Neonatal dengue

Dengue in pregnancy and its adverse outcomes are another example of a severely neglected public health issue. Dengue causes 100 millions of infections annually, 250,000 cases of dengue hemorrhagic fever and 25,000 deaths[88]. The lifelong immunity developed after infection with one of the four virus types is type-specific[1], and progression to more serious disease is frequently, but not exclusively, associated with secondary infection by heterologous types[89]. Dengue transmission is ubiquitous throughout the tropics, with the highest risk zones in the Americas and Asia[90]. Studies reporting prevalence data of dengue infection in pregnant women and adverse pregnancy outcomes are scarce. Data from highly endemic areas have reported a prevalence of dengue infection in pregnancy of 2.5% with a vertical transmission rate of 1.6%[91].

Main adverse pregnancy outcomes reported are preterm births, low birth weight neonates, abortion, stillbirth, dengue illness in newborns or infants and adverse maternal outcomes[91,92].

3.11.3 Zika virus infection

The emerging Zika virus (ZIKV) epidemic that began in Brazil in 2015 has now spread rapidly to more than 30 countries in the Americas and the Caribbean, infecting more than 2 million inhabitants[93,94]. The first major outbreak outside of America occurred in 2007 in the Yap Islands of Micronesia[95] with another large outbreak in 2013 occurring in French Polynesia[96].The WHO predicts that millions of cases of ZIKV are likely to occur in the Americas during the following months. These projections, in conjunction with a possible

association between Zika virus infection during pregnancy and microcephaly cases in newborns[97,98] prompted WHO to declare the epidemic a public health emergency of international concern.

The explosive nature of recent outbreaks and concerning links to Guillain-Barre syndrome and microcephaly are incompletely understood. Incidence data from Brazil indicate that reports of suspected microcephaly in Brazil best correlate with ZIKV incidence around week 17 of pregnancy, although this correlation does not demonstrate causation[97]. Between 2010 and 2014, the whole of Brazil reported an average of 163 children with microcephaly, whereas in 2015, there were 3530 cases reported from 20 states and the federal district, with a particular clustering in Pernambuco state, Northeastern Brazil[99]. The relative importance of sexual transmission of ZIKV and asymptomatic ZIKV infections to the overall burden of transmission[100] is also unknown and further studies are urgently needed to confirm this association and establish the consequences of Zika virus congenital infection[98].

Other pathogens which may be vertically transmitted remain neglected because they occur, almost exclusively, in limited-resource countries. Characteristics of some of those can be found in Table 3.

4.- CHALLENGES IN THE CONTROL OF CONGENITAL AND PERINATAL INFECTIONS IN LOWER-MIDDLE AND LOW-INCOME COUNTRIES

4.1.- PREVENTION OF CONGENITAL AND PERINATAL INFECTIONS IN LOWER-MIDDLE AND LOW-INCOME COUNTRIES

Vaccines are the most effective and cost-saving tools for disease prevention. The public health potential of vaccines to tackle and reduce vaccine-preventable infections is well-known. For instance, rubella virus is a candidate for worldwide eradication because human beings are the only known host and a safe and highly effective vaccine is available. Good proof of this is that endemic transmission in the Americas has been interrupted since 2009[101]. The last WHO recommendations advise to introduce rubella vaccination into the routine childhood immunization schedule and in combination with the vaccination of older age groups who are susceptible to rubella[22]. However, rubella control or elimination goals are yet to be established in the African, Eastern Mediterranean, and South-East Asia regions. While vaccination coverage exceeds 90% in Europe and America, it remains less than 10% in Africa[24]. Of the 55 countries that have not yet introduced rubella vaccine, 41 are African countries[102](Table 3). Vaccination is also the most effective measure to reduce the global incidence of hepatitis B. Compared to other health care interventions, vaccination is, in terms of cost-effectiveness, an economically advantageous option[103]. In 1991, the WHO recommended

that all countries introduce a policy of universal hepatitis B vaccination to prevent and control HBV infection. By the end of 2014, 184 countries had included the hepatitis b vaccine in their national immunization programs. Considering that, in highly endemic areas, hepatitis B is most commonly spread from mother to child at birth and the development of chronic infection is very common in these cases, rapid delivery of the first dose of this vaccine soon after birth is essential[104]. A birth dose has been introduced in 96 countries, reaching up to 80% coverage in the Western Pacific but only 10% in African countries[105] (Table 4). Various candidate CMV vaccine trials have also been conducted in the last decade but, it is unclear, in light of emerging findings on the epidemiology of congenital CMV, whether a CMV vaccine would provide substantial reductions in morbidity[106,107].

Strategies for prevention of non-vaccine preventable congenital infectious diseases such as CMV, HSV or toxoplasmosis are not uniform across different countries or even within a country. Measures which involve prenatal education of pregnant or childbearing women, sexual behaviour measures to avoid HSV-2 or syphilis in pregnancy, hand washing, filtering water, and veterinary public health interventions such as labelling to indicate toxoplasma-free meat and improved farm hygiene to reduce animal infection may be difficult to manage in resource-constrained countries. In these settings, hygiene is limited, national health systems and governments are weak and clinical staff, besides scarce, is not always sufficiently qualified or motivated to reinforce behavioural measures.

Prevention of MTCT strategies in those mothers infected during pregnancy remains a challenge in low-income countries. Inadequate disease surveillance in ANC clinics of pregnant women for hepatitis B, toxoplasmosis, HSV-2, or rubella infection poses an important barrier to the control of congenital infections in these settings, where clinical staff is unaware of the real underlying burden of congenital infections and screening tests are not always available. Other potential congenital infections such as CMV or parvovirus B19 remain neglected because universal screening at the ANC has not yet been established even in high-income countries[108].

Other potential MTCT diseases such as syphilis or HIV, whose screening and treatment policies are better established, have shown moderate to high successes in increasing the number of women diagnosed, after successful introduction of point of care screening methods[109,110]. It is known that antenatal screening for syphilis is cost beneficial and cost effective and penicillin (the drug of choice) is effective, cheap, and readily available, as opposed to treating CS, which is expensive[55]. Screening, detecting and treating pregnant women can also contribute to prevent clinical consequences in these women and their partners. However, given that screening and treatment for preventing MTCT of syphilis is not 100% effective, primary prevention of syphilis in pregnant women is also an important strategy that needs to be addressed to truly eliminate CS.

13

Unfortunately, CS still occurs due to a serious of reasons, including the fact that antenatal visits are too late to avert an adverse outcome, clinicians may not have offered testing, testing may not have been affordable, women may not have followed up or received their test results, treatment may not have been available, or treated women may have been re-infected by untreated sexual partners. All of these reasons mostly occur in the poorest and most resource-constrained settings[111].

Regarding to vertical transmission of HIV, in 2013, 54% of pregnant women in low- and middle-income countries did not receive an HIV test, a key step to accessing HIV prevention, treatment and care[112]. Additionally, in 2014, 73% of all pregnant women living with HIV globally received medicines to prevent transmission to their babies. In the absence of any interventions during these stages, rates of HIV transmission from mother-to-child can range between 15-45%[112]. In 2013 the "Option B+" program was introduced, whereas all HIV-1 infected pregnant and breast-feeding women should begin lifelong antiretroviral therapy regardless of their HIV stage, and it has now become the standard of care, with initiation of treatment recommended as soon as HIV-1 is diagnosed[113]. With improved strategies such as this one for the prevention of mother-to-child transmission, the number of newly infected infants has decreased by 58% worldwide, from an estimated 520,000 in 2000 to 220,000 in 2014; 41% of this decline occurring between 2010 and 2014[114]. The implementation of the use of the newer point-of-care rapid syphilis tests (RST) could be a highly advantageous approach, as they may allow for same-day treatment and address logistical barriers to testing encountered with standard tests[109].It is important to highlight, however, that adequate screening may not necessarily increase the proportion of women adequately treated if the required drugs are not readily available. Regional syphilis screening rates in Haiti, Kenya, Mozambique, and the United Republic of Tanzania were increased with introduction of on-site testing but evaluation showed that there were still obstacles to access treatment[55].

Although screening of Chagas is not fully implemented in high endemic areas, some successful programs of maternal diagnosis and follow-up were conducted in Brazil[115]. In some countries of the Western world, similar programs have been put in place to screen for congenitally transmitted Chagas disease among pregnant women coming from highly endemic areas[116].

Finally, in order to control the unabated Zika virus epidemic, the Pan-American Health Organization (PAHO) and the WHO are now recommending aggressive vector control measures to reduce mosquito populations and avoiding bites, which occur mainly during the day[117].

Current recommendations to prevent malaria, another important cause of MTCT infection, in African pregnant women rely on the use of insecticide treated nets (ITNs) and good compliance with intermittent preventive treatment (IPTp) guidelines[118].

14

4.2.- CHALLENGES IN THE DIAGNOSIS AND TREATMENT OF CONGENITAL AND PERINATAL INFECTIONS IN LOWER-MIDDLE AND LOW-INCOME COUNTRIES

An ideal approach for identification of infected pregnant women would be to screen women during the first trimester with a panel of highly sensitive serological tests for the most common pathogens potentially transmissible to the foetus, and again early in the third trimester.   Another optimal approach would be to retest women who are at high risk or from high prevalence areas closer to delivery as primary infection may occur after initial screening[1-6]. Most of ANC programs in low-income countries do not contemplate the screening for toxoplasma, rubella, HSV, or hepatitis B in pregnant women, which are routinely tested at the ANC of high-income countries[119]. In fact, in rural settings of very poor countries access to ANC may be severely restricted; reasons ranging from fear of medical care to nonexistence of ANC. In addition, neonatal screening of those congenital infections named previously does not exist in these countries[119]. Congenital infections are neglected because there is no awareness of their burden. Diagnosis of children infected with such congenital infections is not straightforward, and differential diagnosis with other common infections of the neonatal period appears challenging [2].

Focusing on specific diseases, early detection of hearing loss resulting for instance from CMV congenital infections, can limit long-term disabilities; Furthermore, PCR-based newborn screening to identify those infected, and thus at risk of *sequelae* deserves consideration. Abnormal cranial computed tomography (CTX) findings are associated with congenital CMV infection and long-term *sequelae*[120]. However, CTX scans cannot be performed routinely in limited-resource settings, and infants with congenital CMV infection presenting with central nervous system disorders (CNSD) may be more likely to remain undiagnosed. However, it would be premature to consider newborn CMV screening in resource-poor settings because the disease burden from congenital CMV and the cost/benefit ratio of long-term follow-up have not been well defined. In addition, the cost and the competing health priorities for these settings make it difficult to envision such a screening program. On the other hand, recommended treatment for congenital CMV is seldom available in low-income countries. Regarding rubella and measles, certain initiatives such as the WHO Global Measles Rubella Laboratory Network created by The Measles and Rubella Initiative, support the elimination of measles and rubella through the introduction of high quality laboratory testing of suspected measles and rubella cases[121]. However conditions for specimen collection, processing and testing can be suboptimal in low-income countries and cause laboratory results to be less accurate.

Although national and international guidelines are more uniform in order to prevent other MTCT diseases such as HIV, the access to diagnosis of HIV in infants is available to a very limited number of children in need,

15

with only 15% of exposed infants in LMIC receiving a virological test[122]. According to the updated WHO guidelines, HAART should be initiated among all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count[113]. Of the estimated 600,000 children who require HAART in sub-Saharan Africa, less than 5% are receiving therapy. Without treatment, about one third of children living with HIV die by their first birthday, and half die by their second[80].

In order to approach other neglected congenital infections such as Chagas, a consensus has been established on the control strategy[123]. Since congenital infection with *T. cruzi* is mostly asymptomatic but may progress to severe chronic Chagas disease later in life and an effective treatment is available within the first year of life (benznidazol or nifurtimox), its early diagnosis is of upmost importance[87]. Conventional tests, such as ELISA, indirect immunofluorescence and indirect hemagglutination are available for diagnosis but its performance depends on good quality testing kits and good laboratory practice[87].

4.3.- THE IMPACT OF HIV IN CONTROL OF CONGENITAL AND PERINATAL INFECTIONS

Perinatal HIV transmission rates have declined in industrialized countries after the introduction of HAART and elective caesarean sections[124]. However, Sub-Saharan Africa remains the region of the world most heavily affected by HIV-1; more than 90% of all children who acquired HIV-1 in 2011 residing in this region[125].

As described above, studies have suggested that perinatal HIV transmission is more frequent among newborns with congenital CMV infection[12]and among HSV-2 seropositive women[11] In addition, MTCT of other viruses highly endemic in sub-Saharan Africa such as HBV, may be increased in children born of HIV infected women[126].

Although WHO recommends that countries should ensure the provision of the Option B+ to all HIV infected pregnant women, many countries in sub-Saharan Africa are still only able to offer single dose nevirapine to prevent HIV perinatal transmission[127]. Measures to strengthen national and international policies should be established, especially in areas where treatment of all HIV-infected pregnant women is not the standard of care. The benefits of treatment may be multiple: reduction of MTCT of HIV and decreasing the incidence of congenital infections such as CMV or HSV-2. Strategies such as the birth dose of hepatitis B vaccine[104] or acyclovir treatment to prevent neonatal herpes[128] should be considered in highly endemic countries for HIV, HBV and HSV.

5.- GLOBAL STRATEGIES TO REDUCE CONGENITAL AND PERINATAL INFECTIONS

ONGOING STRATEGIES TO REDUCE CONGENITAL AND PERINATAL INFECTIONS

Global strategies to reduce congenital and perinatal infections are urgently needed. International institutions such as the WHO, the Global Alliance for Vaccine and Immunization (GAVI), the Measles and Rubella Initiative and other organizations are working together to control and prevent some of these infections (Table 5).

6.- FIVE YEAR VIEW: Strategies and goals to tackle a major public health issue: congenital and perinatal infections in lower-middle and low-income countries

The way forward in the following years should focus on the necessary efforts to reduce congenital infections in high-risk populations. At the international level, prevention of MTCT of infections should be made a health system priority, and links with international groups resulting in focused and coordinated international effort should be encouraged, mainly in highly endemic countries.

GLOBAL STRATEGIES

1.- Access to ANC with emphasis on early access

Access to ANC in resource-constrained countries is highly variable, but may be jeopardized in many settings because of fears of medical care to nonexistence of ANC programs. The first step to reduce congenital infections in these settings is ensuring a universal access to ANC while reinforcing the control of diseases already included and enlarging the screening to other prevalent diseases such as syphilis or HBV .In addition, strengthening health national systems and education of population would also be a main priority.

2.- Surveillance and screening ANC

Monitoring of diseases using effective surveillance tools should be conducted both at the ANC and in post-natal encounters with the newborn, such as for instance during the first vaccination scheduled as part of the expanded program on immunization (EPI). Congenital infections can be prevented by an early detection of infection in pregnant women. Programs promoting safe sex or control of STIs, hygiene, nutritional and

educational measures will prevent maternal infection, but if women become infected only proactive screening programs can detect and prevent the deleterious effects of maternal infections on the foetus. A minimal requirement would be that all women should undergo one screening test in their early pregnancy and if this does not happen they should be tested at delivery. Hence these programs must be implemented during ANC[129].

3.- Control of STIs

Since the incidence of some congenital infections such as congenital syphilis, neonatal herpes, HIV, or hepatitis B is directly related to the prevalence of STIs in the population, strategies aiming to reduce the burden of congenital infections should be complemented by adequate programs to prevent, control and treat STIs.

4.- Surveillance in neonates

Improving the early detection and diagnosis of congenital infections should be a priority if an impact on their associated morbidity and mortality is to be achieved. Additionally, better estimates of the global burden of congenital infections in developing countries are urgently required, so as to highlight the impact that such infections play in the global health scenario. Better training of clinical staff in the diagnosis and management of children with suspected congenital infection, together with enhanced awareness from the general population regarding the burden and risks of congenital infections in their environment should lead to the adoption of better management and preventive strategies.

5.- Diagnosis

There is a need to ensure a wide availability of diagnostic tests for diseases such as HIV, syphilis or HBV, for which there are rapid and well-functioning diagnostic tests [109,110]. Reference laboratories for each region (sentinel laboratory) should be established to offer diagnostic possibilities for diseases, which do not yet have readily accessible or cheap diagnostic schemes.

6.- Treatment

The disassociation between testing and treatment administration observed in HIV and syphilis screening programs can be solved using on-site testing in ANC and allowing early receipt of reports leading to earlier treatment of mothers attending clinics late in their pregnancy. Treatment also should be available at the peripheral health post level.

7.- Vaccines

18

For those vaccine-preventable congenital infections, it appears critical to achieve and maintain high levels of population immunity by providing high vaccination coverage. Since vaccines are supposed to be the most effective measure to prevent infections, endeavours to ensure rubella and birth dose of hepatitis B vaccines introduction in child immunization national programs should be encouraged.

7.- EXPERT COMMENTARY

Although enormous efforts are being made at the international and national levels to reduce the burden of some congenital infections, these infections remain far from a public health priority. The recent Zika virus outbreak and its possible association with microcephaly in children born of women infected during pregnancy, has generated worldwide alarm and has highlighted the lack of global awareness regarding the impact of infections transmitted from mother to child. It therefore appears essential to adequately describe the global and local burden of each perinatally-transmitted infection, through the improvement of maternal and neonatal morbidity surveillance systems at the ANC and child services. Ensuring early diagnosis, treatment and vaccination (when available) as the key preventive strategies are also of paramount importance. In order to achieve an effective surveillance, clinical staff must be trained to suspect cases both in pregnant women and their children, so that reporting of cases becomes routine. More effective diagnostic tests, for which more research is urgently needed, could contribute to achieve this goal. Reference laboratories need to be established, where specimens of suspected cases can be sent, ensuring reliable results and rapid feedback. The measles and rubella laboratory network is a successful example of these reference laboratories[121]. For prompt receipt of results, tested women must return to clinic, or there must be a notification system in place; but unfortunately neither of these generally occurs.

As vaccines stand as the best method to reduce rubella and hepatitis B infections, campaigns to introduce them in paediatric immunization programs must be a high priority in places which have not done yet so. Currently a single manufacturer of measles-rubella vaccine (MRV) exists[121]. Many countries have introduced only measles-containing vaccines (MCV) and rely on donors to pay for theses MCV vaccines. Costs to ensure MRV introduction should be ensured by national and international institutions. Research should also focus in the development of new vaccines against other common and devastating congenital infections, such as for instance CMV and toxoplasmosis. Finally, national governments and international institutions should engage in a collaborative manner to successfully achieve all of these goals.

8.- KEY ISSUES

19

- The TORCH complex typically comprises Toxoplasmosis, Rubella, CMV, HSV and other pathogens including Treponema pallidum (which causes syphilis), and other viruses (HIV, HBV, VZV, parvovirus B19).
- Mother to child transmitted infections remain neglected worldwide and especially in low-income countries where cases of children infected are underreported.
- No specific estimates regarding the global burden of congenital infections and their impact on disability and/or neonatal cause-of-death exist.
- Great burden of congenital disease is assumed in low-income countries where co-infection with HIV or other maternal conditions as malnutrition, malaria or poor hygiene may favour MTCT.
- Vertical transmission of some viruses such as CMV, rubella or HSV may be devastating for the infant but most of these cases are not diagnosed.
- Screening of some of infections such as HIV, syphilis or HBV can be easily done at the ANC level and ensuring early diagnosis and treatment (when available) is the key preventive strategy.
- Effective surveillance can be improved, strengthening local health systems and training clinical staff.Global endeavors are needed to introduce and ensure anti-rubella and anti-HBV vaccines at EPI worldwide and research should be focus to develop new vaccines to avoid other congenital infections.
- Global strategies should be established in order to reduce the burden of congenital infections worldwide and especially in low-income countries.

Funding

This paper was not funded.

Declaration of interest

20

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24

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

These three articles are considered of interest because they provide estimates on the global burden of three congenital infections for which scarce data are available, namely congenital toxoplasmosis, congenital rubella syndrome and syphilis.

* ***Guibert G, Warszawski J, Le Chenadec J *et al.* Decreased risk of congenital cytomegalovirus infection in children born to HIV-1-infected mothers in the era of highly active antiretroviral therapy. *Clin Infect Dis*, 48(11), 1516-1525 (2009).**

This article describes how MTCT of CMV can occur even in women CMV infected before pregnancy.

* **Gonzalez R, Desai M, Macete E *et al.* Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-infected women receiving cotrimoxazole prophylaxis: a multicenter randomized placebo-controlled trial. *PLoS Med*, 11(9), e1001735 (2014).**

This article describes the results of a multicenter clinical trial assessing the efficacy of intermittent preventive treatment for malaria in HIV women.

* * **Kamb ML, Newman LM, Riley PL *et al.* A road map for the global elimination of congenital syphilis. *Obstet Gynecol Int*, 2010 (2010).**

Of considerable interest because it is one of the scarce articles showing a global strategy to eliminate a potential congenital disease such as congenital syphilis.

29

FIGURES AND TABLES

Figure 1. Flow chart diagram for articles selection process.

Records identified through database (DB) search for term "congenital" & "infection" (N=20789)

↓

Records identified through DB search for terms "congenital" & "infection" +"developing" & "countries" +"low-income" & "countries"+ "low-middle income" & "countries" (N=353)

+

Records identified through DB search for "congenital" & "toxoplasmosis" (N=3466)

Records identified through DB search for "congenital" & "cytomegalovirus"(N=2917)

Records identified through DB search for "congenital" & "herpes simplex" & infection" (N=637)

Records identified through DB search for "vertical transmission" & "HIV" (N=8307)

Records identified through DB search for "congenital" & "rubella" (N=3217)

Records identified through DB search for "congenital" & "syphilis" (N=3346)

Records identified through DB search for "congenital" & "varicella" & "syndrome" (N=194)

Records identified through DB search for others congenital infections (Zika, dengue, chagas, N=1100)

Records identified through DB search for "congenital" & "hepatitis b" (N=455)

Records identified through DB search for "congenital" & "parvovirus b19" (N=211)

Full-text articles assessed for eligibility (N=309)

→ **Full-text articles excluded (N=140)**

Language: 35

No relevant outcome: 21

Animals: 15

Insufficient data reported: 62

Quality: 7
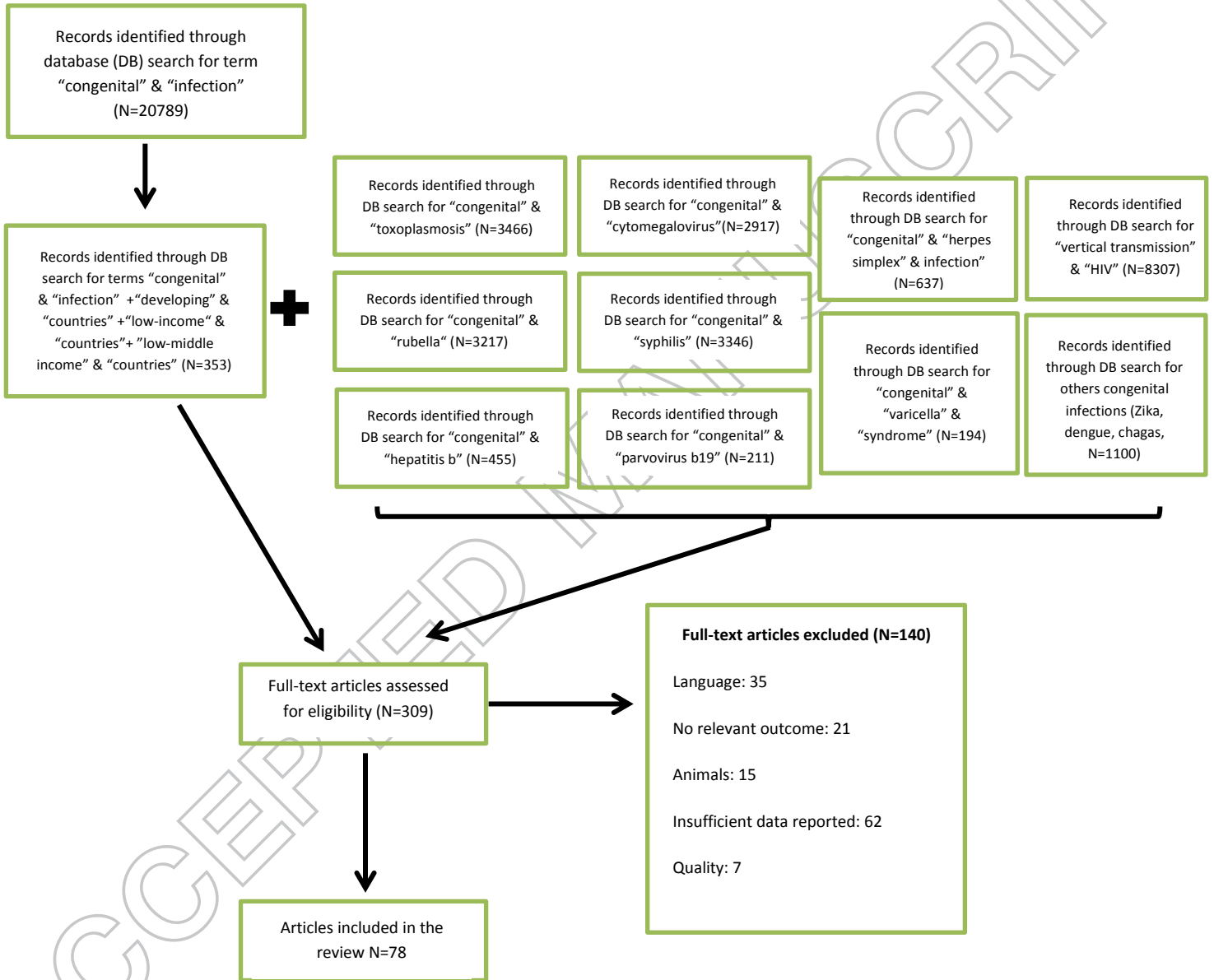
↓

Articles included in the review N=78

Table 1. Commonalities among vertically transmitted infections

Transmission	Cause of infection	Maternal disease	Foetal and/or infant manifestations	Diagnosis
• Placental via • Direct contact during delivery	• Virus • Bacteria • Parasite	• Paucisymptomatic • Asymtomatic • Symptomatic in immunocompromi-sed women	Depending on the timing of the infection: • **< 20 weeks of GA:** more severe illness presentation and may cause multiple malformations. • **Later times of pregnancy:** prematurity, intrauterine growth restriction (IUGR), or central nervous system disorders (CNSD) • **Perinatally:** sepsis, pneumonitis Jaundice, hepatosplenomegaly, thrombocytopenia, etc[2-6].	• Serology • Molecular biology techniques • Cell or pathogen culture

Table 2. Diagnosis, treatment and prevention of some vertically transmitted infections.

31

Disease	Diagnosis	Treatment	Prevention
Congenital Toxoplasmosis	**Mother** *T. gondii*-specific immunoglobuline (Ig) G and IgM followed by the low IgG avidity test **Infant** Definitive diagnosis of congenital toxoplasmosis is made by organism isolation from the placenta, serum, and cerebrospinal fluid (CSF) of infants. Presence of *T. gondii* specific IgM, or persistence of IgG beyond 12 months of age is suggestive of congenital infection[5,130]	Pyrimethamine and sulfadiazine for 1 year +/- Folinic acid [5,130]	**Mother** Improved hygiene and avoidance of raw meat consumption during pregnancy [131,132] *Treatment:* 1. First trimester: Spyramycin 2. Second/ third trimester: Pyrimethamine and sulphadiazine
Congenital Rubella syndrome	Diagnosed based on Rubella-specific IgM, which is usually positive at birth and up to 3 months of age for congenital infection. This diagnosis is confirmed by stable or increasing serum concentrations of rubella-specific IgG over the first 7 to 11 months of life, although false-positive IgM positivity can occur. Low-avidity anti-rubella IgG suggests recent infection. The virus can also be isolated in culture or by PCR, common practice in the Western world[5,21,133-135].	Specific treatment not available. Supportive care.	**Mother** Women of childbearing age and pregnant women should have evidence of immunity to rubella. If they are found to be non-immune, they should be vaccinated with 1 dose [2,135]. **Infant** *Monovalent vaccine:* 1 dose regimen offers high response (≥95%) and long-term protection [136]. *Combination vaccines:* 2 dose regimen. combination with vaccines against measles (MR), measles and mumps (MMR), or measles, mumps and varicella (MMRV).
Congenital CMV infection	Culture-base methods and PCR from saliva, urine, blood and cerebrospinal fluids specimens should be obtained within the first 2 weeks of life to confirm intrauterine infection[137]. A retrospective diagnosis of congenital CMV infection by detecting the presence of CMV-DNA in the dried blood spot samples collected and stored from the neonatal screening period[1]. Serology (IgM anti-CMV and antigenemia) is also diagnostic but must be confirmed by culture or PCR[138].	*First choice*: Ganciclovir and Valganciclovir (val-GCV) [139]. *Others options:* foscarnet and cidofovir [140].	**Mother** Improved hand washing during pregnancy[108]. *Screening:* Antenatal screening of limited impact[108,141]. *Treatment:* -Maternal treatment with oral val-GCV yet to be evaluated[142]. - CMV hyperimmunoglobulin to pregnant women with foetal infection after primary CMV infection[143].
Neonatal herpes	**Mother** Culture and PCR from genital lesions. Serology to distinguish primary infection from reactivation[46]. **Infant** Viral culture (conjunctivae, nasopharynx,	Parenteral acyclovir[46]	**Mother** Prevention of maternal HSV acquisition during pregnancy. *Treatment:* Maternal treatment with

32

	mouth, and anus) is the definitive method to identify newborns with HSV. PCR can also confirm the diagnosis[46]. Little value of serological tests[144]		oral acyclovir[144]. Cesarean delivery. Prevention of postnatal acquisition[46].
Congenital syphilis	According with the WHO guidelines[145]case definitions of CS are: *Probable*: 1) an infant whose mother had untreated or inadequately treated syphilis during pregnancy (regardless of signs in the infant), or 2) an infant or child with a reactive treponemal test and any one of the following: evidence of syphilis infection in the newborn on physical examination, long bone x-rays compatible with CS, a reactive VDRL-CSF, an elevated CSF cell count or protein (without other cause), a reactive FTA-ABS 19S-IgM antibody test, a reactive IgM ELISA, or a reactive IgM treponemal Western blot. *Confirmed*: T. pallidum in darkfield microscopy, fluorescent antibody, or other specific stains in specimens from lesions, placenta, umbilical cord or autopsy material. In recent years, point-of-care rapid diagnostic tests for syphilis have appeared, and could revolution the early recognition of this congenital infection.	**Cases confirmed o probable of CS:** Crystalline penicillin G or procaine penicillin. **Cases not probable or not confirmed**: a single dose of benzathine penicillin[146].	**Mother** *Screening:* Antenatal syphilis screening is highly cost-effective[147]. Diagnostic tests are effective and require minimal logistic support. *Treatment:* Parenteral penicillin G[57].
Congenital varicella syndrome	Diagnosing congenital varicella starts with recognizing the disease in the pregnant mother. VZV can be identified by PCR or by immunofluorescence techniques in skin scrapings or from vesicle fluid. Acute and convalescent IgM titers can diagnose in hindsight but will not identify acute disease[5]	Parenteral acyclovir.[148].	**Mother** *Screening* Immunization is contraindicated during pregnancy[149]. *Treatment:* Acyclovir[149]. **Infant** Post-exposure prophylaxis with immunoglobulin and/or antivirals[148].
Hepatitis B infection	**Mother** The presence of HBsAg signifies that the mother has an acute or chronic. Presence of HBeAg implies higher risk of transmission[150]. **Infant** The diagnosis of HBV infection is based on the detection of viral particles (HbsAg, HbeAg, HBV-DNA) and antibodies (Anti-Hbc IgM, IgG, Anti-HBs).	Lamivudine is approved for treating CHB in children 2 years of age and older[151]. There is no treatment for acute HBV	**Mother** Maternal antiviral therapy[152] **Infant** Hepatitis B vaccine (3 dose-regime)[103] and Hepatitis B Ig prophylaxis[103].

33

	In children exposed to HBV, an HBeAg positive or a high viral load can confirm the diagnosis [64].	infection.	.
Hepatitis C infection	**Mother** Routine screening of pregnant women is not advocated. However, targeted screening in high-risk women is recommended[153] **Infant** *Anti-HCV IgG:* _To test the children after 18 months, since persistence of maternal antibodies can be as long as 18 months. _ *HCV-RNA PCR:* _ May be performed at 1 to 2 months of life and should be repeated after 12 months of age, because up to 30% of infants may clear their infection[153,154].	Interferon-based therapy combined with ribavirin approved for children over 3 years. No indicated in infants[154]	Therapy in pregnant women is not indicated to prevent perinatal transmission[153].
Congenital parvovirus B19	Foetal hydrops and aplastic anemia are highly indicative of intrauterine foetal infection. Anti-B19V IgG and IgM should be investigated in the mother, although maternal IgM may be negative at the onset of hydrops foetalis[155]. Foetal cord blood and amniotic fluid samples are suitable for definitive diagnosis, performed by PCR[156].	Supportive care. Treatment of B19V induced foetal anemia with intrauterine erythrocyte transfusion[157].	Interventions to control and prevent this disease are limited.
HIV infection	**Mother** HIV serological assays should be included in the routine panel of prenatal screening tests for all pregnant women. Repeat screening in the third trimester is recommended in regions with elevated rates of HIV infection among pregnant women[158]. **Infant** *HIV serological assays:* * <18 months of age: used as a screening assay to determine HIV exposure * >18 months of age: used as a diagnostic assay *HIV DNA or HIV RNA:* <18 months of age: used as a diagnostic assay. It should be done to all HIV-exposed infants at 4–6 weeks of age[159].	HAART should be initiated among all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count[113]	**Mother** Option B+: all HIV-1 infected pregnant and breast-feeding women begin lifelong antiretroviral therapy regardless of their HIV stage[113]. **Infant** Daily NVP or AZT from birth through age 4–6 weeks regardless of infant feeding method[160]

34

Table 3. Neglected congenital infections

Organism	Category	Description	Region
Plasmodium (*P falciparum, P vivax, P ovale and P malariae*)	Protozoa	**Neonatal malaria** *P falciparum* and to a lesser extent also *P vivax* are associated with malaria infection during pregnancy. Placental infection ranges between 4.6% and 5.6% in HIV negative women with intermittent preventive treatment of malaria (IPTp)[161] and 7.4% in HIV infected women with no preventive treatment[162]. Prevalences of congenital malaria range from 8% to 33%, but increasing trends of congenital malaria may be the result of increasing drug resistance, increasing virulence of the parasite, HIV, or increased reporting or detection of cases[163]. Associated symptoms in the infant include prematurity/low birth weight, IUGR, still birth, anemia and sepsis-like syndromes[164].	Sub-Saharan Africa More date needed in Asia and the Americas
Mycobacterium tuberculosis	Mycobateria	**Congenital Tuberculosis** The incidence of tuberculosis in pregnant women could be as high as in the general population, but congenital tuberculosis is a rarity. Transmission can be via haematogenous spread through the umbilical vein, or ingestion or aspiration of infected amniotic fluid. Congenital tuberculosis may simulate bacterial/viral sepsis or other congenital infections such as syphilis and human cytomegalovirus infection[165].	Worldwide

Table 4. Available vaccines against pathogens potentially causing congenital infections

Organism	Type of vaccine	Coverage by WHO region	Countries that have introduced vaccine by region		
Rubella			**WHO region** [102]	**YES**	**NO**
	Combination vaccine→ Measles and Rubella(MR)	- 140 countries by the end of 2014 (of 194 countries members of WHO) - Global coverage 46% in 2014 * 90% America and Europe *<10% Africa[105]	Africa	6	41
			America	35	0
			East Mediterranean	15	6
			Europe	53	0
			South East Asia	6	5
			Western Pacific	24	3
			TOTAL	**139**	**55**

35

Hepatitis B			Data not available	
	1.- Monovalent vaccine→ birth dose	- 184 countries by the end of 2014 (of 194 countries members of WHO)		
	2.- Pentavalent vaccine→ Hepatitis B+DTPa+Hib	- Global coverage of 3 doses 82% in 2014 - Birth dose was introduced in 96 countries by 2013 *Global coverage 38% *Western Pacific 80% * Africa 10%[105]		
Varicella			Data not available	
	1.- Monovalent vaccine	-A limited numbers of industrialized countries have introduced varicella vaccination into their childhood immunization programs[166].		
	2.- Combination vaccine→measles +rubella+mumps (MMR)+ varicella	- No data of routine childhood varicella vaccination found in low and middle income countries.		

Table 5. Strategies to reduce congenital infections currently on-going

Disease	Strategies to fight against the disease	Goal	Institutions involved	Region
Rubella[121]	1.- Achieve and maintain high levels of population immunity by providing high vaccination coverage, including mass immunization of adolescent and young adults (male and females) as carried out in the Americas[167]. 2.- Monitor disease using effective surveillance and evaluate programmatic efforts to ensure progress→ Measles and Rubella Laboratory Network. 3.- Develop and maintain outbreak preparedness, respond rapidly to outbreaks and manage cases. 4.- Communicate and engage to build public confidence and demand for immunization. 5.- Perform research and development needed to support cost-effective operations and improve vaccination and diagnostic tools	To achieve rubella elimination in at least 5 (of 6) WHO regions by the end of 2020	**WHO MRI GAVI**	Worldwide
Congenital Syphilis[168]	1.- Ensure advocacy-sustained political commitment to achieving goal of elimination CS. 2.- Increases access to, and quality of, maternal and newborn health services ensuring that all pregnant women are adequately screened and treated and decrease the frequency of missed opportunities for screening women outside maternal and newborn care. 3.- Use of diagnostic test that are effective, affordable and require minimal logistical support, with effective management of all infected women and their partners and the treatment of infants born to seropositive mothers. 4.- Establish surveillance, monitoring and evaluation systems (improving surveillance systems, developing indicators and strengthening	To achieve congenital syphilis elimination.	**WHO**	Worldwide

36

	monitoring and evaluation systems)			
Hepatitis B [104]	Introducing hepatitis B vaccine (3 doses) including birth dose into national immunization services.	Controlling HBV worldwide to decrease the incidence of HVB-related chronic liver disease and hepatocellular carcinoma, more likely become in person infected during infancy.	**WHO GAVI**	Worldwide
Congenital Toxoplamosis[169,170]	Maternal Screening Program	To reduce the rate of vertical transmission and/or foetal development impairment	**National health systems**	Some countries in Europe (Austria, France, Slovenia, Germany, Italy, Spain, Belgium) and some states of Brazil.
	Neonatal Screening Program	To reduce sequelae in infected newborn		Poland, Denmark, some states of US and some states of Brazil

WHO: World Health Organization; GAVI: Global Alliance for Vaccination and Immnunization. MRI: The Measles and Rubella Initiative. CS: Congenital syphilis