The status of syphilis in pregnant women in Brazil: do we need a national (or world?) day of syphilis combat? Is syphilis a public health problem only in Brazil?

AN OLD PROBLEM

In his verses in the book *Syplilis Sive Morbus Gallicus* (Verona, 1530), in which the word *syphilis* appears for the first time, Hieronymi Fracastorii anticipated that this disease would persist:

> From the purple belly of the night, a slave/ The strangest plague came back to ravage the world/ Infecting the heart of Europe, the plague was thrown/ From Lebanon to the waves of the Black Sea/ When, in war, France marched through Italy/ The disease took its name. I'll dedicate my rhymes to this intruder of twenty pests / That, even if it is not welcome, is eternal since it intends to remain here[1].

Nowadays syphilis continues to plague many countries in the world despite the discovery of penicillin.

In 1905, *Treponema pallidum* subsp. *pallidum* (*T. pallidum*) was identified by Schaudinn and Hoffmann as an etiological agent of syphilis. This motile bacteria, similar to Gram-negative, is environmentally fragile, microaerophilic, with a spiral-shaped structure in a length of 6–20 μm[2].

Syphilis is a chronic and systemic infectious disease that is transmitted sexually or via other types of intimate contact. It may be transmitted from mother to fetus (intrauterine) or through contact between mother and child during birth[3]. Global prevalence for this disease in pregnancy is about 0.5% (0.2 to 1.8%)[4].

The infection can be categorized as recent (primary and secondary), latent (early or late) or late. All stages can occur during pregnancy. Gestational syphilis is estimated in about two million a year, mostly in developing coutries. Less than 10% of these cases are diagnosed[5].

Specifically in Brazil, the Ministry of Health indicates that, in the last five years, the number of syphilis cases has risen in pregnant women, congenital and acquired, partially attributed by the increase of test coverage, the expansion of tests' use , less use of condom, resistance of health professionals to administrate penicillin in primary care and lack of penicillin supply[6]. The underreporting of acquired syphilis cases and inadequate treatment of partners are of particular concern, because they are closely associated with a large occurrence of this disease during pregnancy.

In 2016, 87,593 cases of acquired syphilis, 37,436 cases of syphilis in pregnant women and 20,474 cases of congenital syphilis — among them, 185 deaths — were reported in Brazil. The rate of detection was of 12.4 cases of syphilis in pregnant women per 1,000 live births. Southern and Southeastern states registered the highest rates (16.3 and 14.7 cases, respectively)[6].

The higher rates on Congenital syphilis' rates than on syphilis during pregnancy's show that there is still much to be done for proper diagnosis and treatment during pregnancy. Even worse is that, in 2016, 81.0% of mothers of children with congenital syphilis reported to have prenatal care. Cities like Teresina, Fortaleza, Natal, João Pessoa, Recife, Maceió, Aracaju (Northeast) and Porto Alegre (South) registered more cases of congenital syphilis than syphilis-during pregnancy[6]. This information clearly indicates inadequate prenatal monitoring and lack of diagnosis in pregnant women.

The lack of penicillin in 2016 has caused a major disorder and is partly responsible for the increase in the number of cases. The opening of the Brazilian market and the early signature of trade agreements involving active pharmaceutical inputs in the 1990s showed that Brazilian drug productionwas not competitive at global level. With lower taxes, buying products abroad led to higher profits. Multinational companies operating in Brazil abandoned their production or transferred this stage to branches elsewhere, where the cost of production, including labor ones, was much cheaper. This change devastated Brazilian pharmochemicals' manufacture[7].

To make matters worse, both private and public companies, as well as public health managers, haven't made an adequate plan to maintain strategic stocks of penicillin and other drugswidely used in Brazil.

Similar facts about the lack of penicillin have occurred in other countries. Even the United States, world's largest economy and place of extremely high industrial and scientific development, faces difficulties with the normal use of penicilin. On its website, the Centers for Disease Control and Prevention (CDC) present a roadmap for the rational use of penicillin[8].

However, the high numbers of syphilis cases in Brazil and the lack of planning have made penicillin scarce, especially for its use in pregnant women. It is a true national embarrassment.

Without any clarification for a better understanding, injectable veterinary products with high doses of crystalline penicillin, procaine and benzathine in a single bottle, were never missing in Brazil and did not present any contingencies in 2018.

CDC considers that pregnant women must have access to early prenatal care and be serologically tested for syphilis at their first prenatal visit. In high risk areas, it should be doneonce more at 28–32 weeks pregnancyand at childbirth[9].

The Brazilian Ministry of Health uses three flowcharts aiming at assisting and standardizing immunological diagnosis of syphilis. Two or more combined tests form a flowchart. This combination of sequential testing aims to increase the positive predictive value (PPV) of a reagent result in the initial test. The flowchart in series is logical and cost-effective[10]. Flowchart 1 consists in the conventional approach for syphilis diagnosis by immunological tests, in which a nontreponemal test is used as the first one, followed by a treponemal test to confirm diagnosis. Flowchart 2 embraces unconventional approach for syphilis diagnosis by immunological

tests, in which a treponemal test (Enzyme-Linked Immunosorbent Assay — Elisa, chemiluminescence or other equivalents) is used as the first test, followed by a nontreponemal test to confirm diagnosis. Flowchart 3 encompass unconventional approach for syphilis diagnosis by immunological tests, in which a rapid treponemal test is firstly used, followed by a nontreponemal test for diagnosis confirmation. However, if the nontreponemal test is non-reactive, Flowchart 3 recommends the use of a third treponemal laboratory test.

A therapeutic alternative for primary syphilis, secondary and early latent syphilis (up to one year) is: Penicillin G benzathine, 2.4 million internacional units (IU), intramuscular (IM), single dose (1.2 million IU in each gluteus). As another option, there is: Ceftriaxone 1g, IV or IM, once a day, for eight to ten days for pregnant and non-pregnant women. In later latent syphilis (more than one year of duration) or latent with unknown duration and tertiary: Penicillin G benzathine, 2.4 million IU, IM (1.2 million IU in each gluteus), weekly, for three weeks. Total dose of 7.2 million IU. As alternative: Ceftriaxone 1 g, IV or IM, once a day, for eight to ten days for pregnant and non-pregnant women[11].

Treatment during pregnancy

Adverse pregnancy outcomes are common in women with syphilis[12,13], so the treatment should be provided as soon as possible.

A study carried out in Tanzania found that 25% of women with latent syphilis who had rapid plasm reagin (RPR) titres ≥1:8 gave birth to a stillborn child, and 33% had a preterm birth[14]. A second study (still in Tanzania written by the same researchers) showed that adverse pregnancy outcomes due to syphilis can be prevented with a single dose of benzathine penicillin G before 28 weeks of pregnancy[15]. Treatment with penicillin G benzathine before the 28th week of gestation was one of the most cost-effective interventions available for saved lifetime[16].

However, World Health Organization (WHO) recommends that children with suspected congenital syphilis, including the oneswhose mothers are seropositive for syphilis and not treated with penicillin >30 days before childbirth, should be treated with aqueous benzyl penicillin or procaine penicillin[17]. Beyond that, every child exposed to syphilis, even the ones with no signs or symptoms at birth, should be closely monitored, ideally with non-treponemal test (NTT) titres. Titres should decline by 3 months of life and be nonreactive by 6 months[18]. Treponemal tests (TTs) are not useful in children due to persistent maternal antibodies[18].

Aware of the seriousness of the situation, the Brazilian Ministry of Health created the Strategic Actions Agenda to Reduce Syphilis in Brazil, a collective work with associations of class. Besides, with the objective of emphasizing the importance of adequate diagnosis and treatment for syphilis as a sexually transmitted disease,especially in pregnant women during prenatal care, Brazilian government sanctioned the Federal Law No. 13,430 of March 31, 2017, creating through Law 13,430 / 2017 the National Day for Fighting Against Syphilis[19]. It was a response to a lawsuit commenced by the Brazilian Society of Sexually Transmitted Disease (STD) and the STD Sector of Federal Fluminense University, which in 2004 started a national movement to combat syphilis.

This law establishes that every year, on the third Saturday of October, there must be multiple activities (scientific, educational, dissemination) throughout the country, aiming at acquired and congenital syphilis combat[20].

Considering that syphilis represents an old and continuous problem for public health all over the world, we propose that this Brazilian attitude should be extended to a Global Day for Syphilis Combat. Thus, it is possible to give greater visibility to the serious problems and deaths (abortions, stillbirths and newborn death) caused by this disease.

In the sense that many complications involving syphilis may still appear, we refer to Rekart et al,[21] to the increase in syphilis cases in men who keep sexual relations with other men (MSM) and are submitted to highly active antiretroviral therapy (HAART) for human immunodeficiency virus 1 (HIV-1) infection.

The authours speculate

The prevailing hypothesis is that HAART availability and effectiveness have led to the perception among both individuals who are HIV-1 infected and those who are uninfected that HIV-1 transmission has become much less likely, and the effects of HIV-1 infection less deadly. This is expected to result in increased sexual risk-taking, especially unprotected anal intercourse, leading to more non-HIV-1 STDs, including gonorrhoea, chlamydia and syphilis. However, syphilis incidence has increased more rapidly than other STDs[21]. These authors consider that HAART regulates innate and acquired immune responses to *T. pallidum* and that this biological explanation has an important role in syphilis epidemic.

HIV has evolved with a significant repertoire of mechanisms that target autophagy[22], and who knows if these mechanisms may be connected with the growth of syphilis cases in MSM HIV-1 positive using HAART?

Considering that antiretroviral drugs are increasingly used worldwide in HIV treatment and in pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) actions, side effects may interfere in epidemics of other STDs.

Syphilis in pregnancy time, although known and well defined, is still a global challenge, especially for developing countries. Intense and well-planned actions must be taken by all agencies involved to reduce the incidence of the disease, otherwise we will continue observing serious complications and death of concepts.

In attention to pregnant women with STDs, it is necessary to get rid of some old habits, like the gynecologist / obstetrician who only attends the woman but doesn't administer treatment during consultation. When prescribing penicillin injections to be taken at another time and not calling patient's sexual partner for first and immediate care, the doctor is deferring the best attention to interrupt transmission chain and prescribe the appropriate treatment.

More than attending a pregnant woman, the doctor and the whole team of health professionals should welcome the pregnant woman, her sexual partner and her family. For only then, it will be possible to break the prejudices (and contagions) that involve STDs, especially syphilis.

To complicate syphilis combat in Brazil, many basic health care services do not apply penicillin in patients. For years, we've had

a standard set by Brazil's Federal Nursing Council that indicated that penicillin should only be applied to medical services that had cardiopulmonary restraint stalls in order to revert a possible anaphylactic shock.

This standard was discared by the Ministry of Health, but, unfortunately, in our everyday life, we have not yet achieved the objective of applying penicillin in all Brazilian basic health units.

Another serious problem is the delay with serological tests results. Often, Venereal Disease Research Laboratory (VDRL) result takes more than 30/40 days.

As many women arrive at their first consultation in the second trimester of pregnancy, the delay to perform exams and result's awareness cause the treatment to be performed near childbirth. The later syphilis treatment is to birth, the higher the chances of congenital syphilisor another serious outcomes.

In 2012, data from WHO estimated the existence of 17.7 million people with syphilis, with 5,590,000 cases of syphilis every year. The numbers by region are: 440,000 in Europe; 496,000 in Eastern Mediterranean; 886,000 in South-Eastern Asia; 937,000 in America; 993,000 in Western Pacificand 1,843,000 in Africa[4].

In many countries, especially in low-income ones, the mother-to-child transmission (MTCT) remains very high and it is a common cause of death[23,23].

Syphilis, after malaria, is the most frequent etiology of avoidable stillbirth in the world[25].

Working with data from the Brazilian Information System for Notifiable Diseases (SINAN), available at the Health Portal of Brazilian Ministry of Health (http://portalsinan.saude.gov.br/ sifilis-em-gestante and http: // portalsinan. saude.gov.br/sifilis-congenita), Saraceni et al.[26] performed a detailed analysis of reports of syphilis in pregnant women and congenital syphilis in six federative units (states) in Brazil. The authors summarize the main results:

> The rate of detection of syphilis in pregnant women grew between 21% (Amazonas) and 75% (Rio de Janeiro). The incidence of congenital syphilis followed the same increase profile, varying from 35.6% in the Federal District to 639.9% in Rio Grande do Sul, with a 0.7% reduction in Amazonas. The performance of prenatal care in women with congenital syphilis outcome ranged from 67.3% in Amazonas to 83.3% in the Federal District. Of the pregnant women with syphilis, 43% had a reported outcome of congenital syphilis. In pregnant women with syphilis and outcome of congenital syphilis, maternal diagnosis occurred during prenatal care in 74% and delivery in 18%. In 8% of the women the diagnosis was ignored.

They also say that these rates may have been led by increased report of cases[26].

Milanez[27], reflecting on the Brazilian capacity to face this problem, says that recent data on syphilis during pregnancy and congenital syphilis in Brazil are alarming. A significant proportion of women and newborns are infected. There was an increase of 1,047% between 2005 and 2013 among pregnant women. During the same period, increase of 135% in congenital syphilis notifications was observed. These numbers might indicate an improvement on notification, which has happened in fact. Nevertheless, it is not enough to explain the number of cases in pregnant women and newborns[27].

The same situation happens in other countries of Latin America and the Caribbean, and it is a must to improve the capacity of countries to collect high-quality data about interventions and inequalities, and to use this data as a basis for a set of decisions to improve pregnant women and children's care[28].

As most of Brazilian mentioned publications work with information from the database of compulsory notification sheets, we believe that it is necessary to cite authors who have worked with syphilis problems in pregnant women and congenital syphilis in their local medical services. The data of these surveys reveal that reality can be much more serious and worrying than the official statistics show. We will present some recent studies from several Brazilian regions.

In a retrospective, prospective, comparative, cross-sectional and observational study of congenital syphilis (CS), the occurrence of cases was observed in two different periods with 512 puerperal women in each one (2006 and 2011), with a total of 1,024 puerperal women from four maternity hospitals in the city of Campo Grande (Mato Grosso do Sul — center-west of Brazil). Figueiró-Filho et al.[29] reported that the prevalence of CS in the first period (2006) was of 2.3% and in the second (2011) 0.58%. On the other hand, the authors observed a significant association between the periods studied and an increase in the frequency of infectious and STDs, from 3.5% (2006) to 10.1% (2011). CS coefficient found for 2006 was 23.4 cases per thousand live births and 5.85 for 2011, which indicates a decrease in the second period. However, it is still ten times higher than the 0.5 rate required for CS elimination.

Cerqueira et al.[30], in a cross-sectional study, pointed out that the prevalence of syphilis in pregnant women was 4.1% in 2012, 3.1% in 2013 and 5% in 2014, with official reporting of 15.6, 25.0 and 48.1%, respectively. This data was collected from 2,041 parturients who had undergone treatment between 2012 and 2014 in the maternity of Pedro Ernesto Hospital of the State University of Rio de Janeiro, in the metropolitan area of Rio de Janeiro. CS incidence was 22/1,000 live births in 2012; 17 in 2013 and 44.8 in 2014. CS underreporting during this period was 6.7%. Vertical transmission occurred in 65.8% of infected mothers' children. It was concluded that in 34.6% of CS cases maternal VDRL titers were of 1/4. Vertical transmission happened in two consecutive pregnancies, one of which being within the low titers group (=1/4). The results also demonstrate the magnitude of the disease, the fragility of the reporting system in assessing its actual prevalence and itsimpact on perinatal outcomes. Moreover, it is a warning about the real situation of syphilis, still underestimated in the state[30].

Holzmann et al.[31] reported, based on data from 107 cases of congenital syphilis in a municipality of the state of Minas Gerais, Brazil, in the period of 2014 and 2015, that 93.5% of these mothers underwent prenatal care, 13.2% of newborns had a diagnosis of neurosyphilis, 23.6% of newborns used drugs other than penicillin, 11.7% of newborns were not referred to outpatient support, only 24.3% were notified, and in 52,3% of all cases there was an inadequate management of newborns, according to the standards recommended by the Brazilian Ministry of Health[31].

Regarding serologies coverage for HIV and syphilis in pregnant womenfrom the private medical service in the state of Rio Grande

do Sul, the percentage of HIV tests performed in childbirth in 2014 was 83.4%, and in 2016 95.8%. In 2014, syphilis exams' coverage was 29%, reaching 82% in 2016. In abortion cases, coverage in 2014 was 55.3% for HIV tests and 86,5% in 2016. In reference to syphilis' examination in cases of abortions, in 2014 24.2% of the cases were examined; and in 2016 this number grew to 73.8%

It is clear that even in private institutions the attention to syphilis is far from ideal. What's more, serology coverage for HIV is always higher than it is for syphilis[32].

Campos et al.[33] analyzed 69 compulsory notification sheets (CNS) in Foz do Iguaçu. From them, nine (13.04%) pregnant women did not perform prenatal care and two (2.90%) were ignored.

Regarding diagnosis of syphilis in pregnant woman, 49 (71.01%) were during prenatal care, nine (13.04%) at the time of childbirth, five (7.25%) after childbirthand three (4.35%) were ignored.Only 10 (14.49%) of all pregnant women were adequate to the treatment.

In reference to newborns with CS, 21 (31.34%) did not undergo any treatment, 21 (31.34%) were ignored, 16 (23.18%) were treated with benzathine penicillin, remaining nine (13, 04%) with another scheme, and two (2.90%) without registration[33].

A descriptive study was carried out using data from confirmed cases of gestational syphilis and CS in Bahia state, Brazil, from 2007 to 2015. This information was obtained from the national database of Brazilian Public Health System (Departamento de Informática do Sistema Único de Saúde — DATASUS). With respect to children with CS, only 6.9% (204/2,948) presented register of an appropriate maternal treatment[34].

With the objective of identifying if Brazilian municipalities (5,300) administered penicillin in 100% of pregnant women with prenatal syphilis, Gonçalves et al.[35] verified that only 52% of the basic health units matched this criteria. This data was obtained from the Program for Improvement and Quality of Life (PMAQ), in order to elaborate a document of good practices concerning these practices, as well as improving the quality of CS' treatment. This result indicates an enormous failure in all prenatal care. About this experience, Brazilian Ministry of Health prepared a document entitled *Good practices booklet: the use of penicillin in basic care to the prevention of congenital syphilis in Brazil*, with the purpose of improving the effectiveness of patients' care , especially pregnant women, with syphilis[35].

This effort makes clear the size of the problem in order to face the effective treatment of syphilis in our country. Detecting who does not apply penicillin in pregnant women at basic health units is essential. Preparing a document for good practices is a great step forward. But to rightly deal with the situation, there are no simple or fast measures. However, it is good that we have already started the job.

For many people, there is still a myth that STDs affect only those from high-risk behavioral groups and / or people of low socio-economic and cultural backgrounds. STDs actually affectthose who have sexual activity and at some point maintain unprotected relationships with an infected person.

In most of the time we use public services' data.

This year we started a project to study the seasonality of anti-HIV and syphilis tests in one of the most traditional supplementary / private clinical laboratory in Rio de Janeiro, which attends, in total, people of high socioeconomic and financial level. Class A, even.

Initial data has high rates of serological reactant results and are surprising, especially for syphilis.

Data from the Richet Laboratory show that in the last years the percentages of positive anti-HIV tests are decreasing: 2.36% (186/7,885) in 2013; 2.04% (199/9,763) in 2014; 1.64% (203/12,397) in 2015; 1.84% (230/12,490) in 2016; and 1.82% (320/17,621) in 2017.

However, syphilis rates show stability: 1.71% (273/15,967) in 2013; 1.56% (310/19,860) in 2014; 1.67% (378/22,679) in 2015; 1.24% (278/24,449) in 2016; and 1.48% (364/42,562) in 2017.

The question is: how many countries in the world have these high syphilis rates in their public and private services?

In Brazil, about 30% of the population does not seek public services in their routine because they have assistance to supplementary medicine (private health plans). In Rio de Janeiro, this share is 40% higher. It is possible to say that the absolute majority of cases of syphilis treated in this segment of health care is not notified to surveillance services of their municipalities. Thus, the numbers of syphilis in Brazil are way different from those ones presented in official data. While we see that, every day we are improving our data on compulsory notifications of infectious diseases.

VACCINES AGAINST SYPHILIS

Genomic sequencing of *T. pallidum* collected directly from samples of recent clinical lesions of syphilis (primary and secondary) is already possible and may overcome the limitation of *T. pallidum* culture and determinants of its virulence[36,37].

Such action can help in developing possible vaccines. Recently, Lithgow et al.[38] showed that immunization of rabbits with lipoprotein TP0751 prevented the spread of *T. pallidum* and thus became a promising vaccine candidate[38].

REFLECTING

Our intention with this article was not to just talk about traditional scientific issues.

What illness has a five-century book that describes it[1]? Have you had an etiologic and serological diagnosis for over 100 years[2]? Have you had a safe and highly effective treatment for more than 70 years[39,40]? Have you studied the natural history of the disease in human experiments for more than 70 years and then a president apologized for these studies on behalf of the nation[40]? Do you make reservations for the lay public based on real facts transformed into a movie, watched until today and serving as material for medical ethics classes around the world[41,42]?

We need to get out of the simplistic lines of safe sex, condom distribution during Carnival, rapid tests in public squares, but we should encourage of open and unprejudiced dialogue, seeking reflection in high school and university institutions several times over the years. It is necessary to have frequency and a sequence of educative actions. Simple tactics have not been working for decades, at least in our country.

Simply say that: every pregnant woman should be tested for syphilis at her first visit at a doctor; her sexual partners should be examined, tested and treated (when necessary) in conjunction with the woman; the administered drug must be penicillin;

if there is a history of allergy to penicillin, the hypersensitivity test should be performed and, if confirmed, desensitization should be done immediately, and, if there are no conditions for these actions to occur, a penicillin dose should be applied in a safe environment. These discourses should get into the daily routine of medical attention.

The Brazilian example of the HPV-vaccine application of the with 100% coverage on adolescents in schools is a milestone.

The coverage of the second and third HPV doses fell by half when schools decline to participate — to the point of the expressive quantity of expired vaccines on refrigerators' shelves in vaccine rooms throughout Brazil, without being applied in Brazilian adolescents.

We hope that more public health managers, educators, representatives of civil organizations, people from the general population, directors from different media sectors, research groups, as well as more companies, invest especially in the awareness of responsibilities with human relationships so that the words of Fracastorii, in 1530, at the beginning of this article, are considered as only an outdated historical verse.

As for Brazil and many other countries in the world to be aware that health education process is based on schools andnot in isolated advertising. To the title of this article we respond yes.

When we were finishing the review of this editorial, we found the article by Takahashi et al reporting the rapid increase in cases of syphilis, including congenital syphilis, in Japan: "Among women, 20- to 24-year-olds consistently had the highest reporting rate, reaching 9.0 per 100,000 in 2016. Although Tokyo prefecture had the highest reporting rate (3.98 per 100,000 person-years)"[43].

And they end up saying that, currently, syphilis is a major public health problem in Japan[43].

MAURO ROMERO LEAL PASSOS
MD, PhD, Full professor. Chief of the Sexually Transmitted Diseases Sector, Department of Microbiology and Parasitology – Universidade Federal Fluminense, Niterói, Brazil.
E-mail: mauroromero@id.uff.br

JOSÉ ELEUTÉRIO JUNIOR
MD, PhD, M.I.A.C. Associate Professor, Department of Maternal and Child Health – Universidade Federal do Ceará, Fortaleza, Brazil.
E-mail: prof.eleuterio@gmail.com

PAULO CESAR GIRALDO
[3]MD, PhD. Full professor, Department of Obstetrics and Gynecology, Faculty of Medical Sciences – Universidade Estadual de Campinas, São Paulo, Brazil.
E-mail: paulocesargiraldo@gmail.com

REFERENCES

1. Fracastorii H. Syplilis Sive Morbus Gallicus. Verona; 1530.
2. Stamm LV. Syphilis: Re-emergence of an old foe. Microb Cell. 2016;3(9):363-70. https://dx.doi.org/10.15698%2Fmic2016.09.523
3. Passos MRL, Almeida Filho GL, Coêlho ICB, Moreira LC, Nahn EP Jr, José Eleutério J Jr. Atlas of Sexually Transmitted Diseases Clinical Aspects and Differential Diagnosis. Cham: Springer International Publishing AG; 2018.
4. Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N, et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. PLoS One. 2015 Dec 8;10(12):e0143304. https://dx.doi.org/10.1371/journal.pone.0143304
5. Macêdo VC, Lira PIC, Frias PG, Romaguera LMD, Caires SFF, Ximenes RAA. Risk factors for syphilis in women: case-control study. Rev Saúde Pública. 2017 Aug 17;51:78. https://dx.doi.org/10.11606/S1518-8787.2017051007066
6. Brazil. Secretaria de Vigilância em Saúde. Ministério da Saúde. Boletim Epidemiológico. 2017;48(36).
7. Ciscati R. Por que o Brasil não tem penicilina. Época [Internet]. 2017 [cited on Jan 1, 2018]. Available from: https://epoca.globo.com/saude/check-up/noticia/2017/06/por-que-o-brasil-nao-tem-penicilina.html
8. Center for Control Diseases and Treatment. Penicillin G benzathine (Bicillin-LA) Shortage [Internet]. 2016 [cited on Jan 29, 2018]. Available from: https://www.cdc.gov/std/treatment/drugnotices/bicillinshortage.htm
9. Syphilis during pregnancy. 2015 Sexually transmitted diseases treatment guidelines [Internet]. Atlanta: Centers for Disease Control and Prevention; 2015 [cited on Jan 6, 2015]. Available from: http://www.cdc.gov/std/tg2015/syphilis-pregnancy.htm
10. Brazil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância, Prevenção e Controle das Doenças Sexualmente Transmissíveis, Aids e Hepatites Virais. Manual Técnico para Diagnóstico da Sífilis. Brasília: Ministério da Saúde; 2016.
11. Brazil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância, Prevenção e Controle das Doenças Sexualmente Transmissíveis, Aids e Hepatites Virais. Protocolo Clínico e Diretrizes Terapêuticas para Atenção Integral às Pessoas com Infecções Sexualmente Transmissíveis. Brasília: Ministério da Saúde; 2015.
12. Gomez GB, Kamb ML, Newman LM, Mark J, Broutet N, Hawkes SJ. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. Bull World Health Organ. 2013;91:217-26. https://doi.org/10.2471/BLT.12.107623
13. Qin J, Yang T, Xiao S, Tan H, Feng T, Fu H. Reported estimates of adverse pregnancy outcomes among women with and without syphilis: a systematic review and meta-analysis. PLoS One. 2014;9:e102203. https://doi.org/10.1371/journal.pone.0102203
14. Watson-Jones D, Changalucha J, Gumodoka B, Weiss H, Rusizoka M, Ndeki L, et al. Syphilis in pregnancy in Tanzania. I. Impact maternal syphilis outcome pregnancy. J Infect Dis. 2002;186:940-7. https://doi.org/10.1086/342952
15. Watson-Jones D, Gumodoka B, Weiss H, Changalucha J, Todd J, Mugeye K, et al. Syphilis in pregnancy in Tanzania. II. The effectiveness of antenatal syphilis screening and single-dose benzathine penicillin treatment for the prevention of adverse pregnancy outcomes. J Infect Dis. 2002;186:948-57. https://doi.org/10.1086/342951
16. Terris-Prestholt F, Watson-Jones D, Mugeye K, Kumaranayake L, Ndeki L, Weiss H, et al. Is antenatal syphilis screening still cost effective in sub-Saharan Africa. Sex Transm Infect. 2003;79:375-81. https://dx.doi.org/10.1136%2Fsti.79.5.375
17. Peeling RW, Mabey D, Kamb ML, Chen X-S, Radolf JD, Benzaken AS. Syphilis. Nature Rev Disease Primers. 2017;3. https://dx.doi.org/10.1038/nrdp.2017.73
18. Workowski KA, Bolan GA, Centers for Disease Control & Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR. 2015;64:1-137.
19. Brazil. Senado Notícias. Lei cria o Dia Nacional de Combate a Sífilis e à Sífilis Congênita [Internet]. 2017 [cited on Jan 31, 2018]. Available from: https://www12.senado.leg.br/noticias/materias/2017/04/03/lei-cria-o-dia-nacional-de-combate-a-sifilis-e-a-sifilis-congenita
20. DST UFF. Setor de DST – UFF [Internet]. [cited on Jan 31, 2018]. Available at: https://www.facebook.com/dst.uff.7/videos/1890325867645999/
21. Rekart ML, Ndifon W, Brunham RC, Dushoff J, Park SW, Rawat S, et al. A double-edged sword: does highly active antiretroviral therapy contribute to syphilis incidence by impairing immunity to Treponema pallidum? 2017. https://dx.doi.org/10.1136/sextrans-2016-052870

22. Athanasiou A, Leizer J, Minis E, Linhares IM, Witkin SS. Manipulation of autophagy by sexually transmitted infections: new opportunities for intervention. J Bras Doenças Sex Transm. 2017;29(1):5-7. https://dx.doi.org/10.5533/DST-2177-8264-201729102
23. 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:e1001396. https://doi.org/10.1371/journal.pmed.1001396
24. Wijesooriya NS, Rochat RW, Kamb ML, Turlapati P, Temmerman M, Broutet N, et al. Global burden of maternal and congenital syphilis in 2008 and 2012: a health systems modelling study. Lancet Glob Health. 2016;4:e525-33. https://doi.org/10.1016/S2214-109X(16)30135-8
25. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C. Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet. 2016;387:587-603. https://doi.org/10.1016/S0140-6736(15)00837-5
26. Saraceni V, Pereira GFM, Silveira MF, Araujo MAL, Miranda AE. Vigilância epidemiológica da transmissão vertical da sífilis: dados de seis unidades federativas no Brasil. Rev Panam Salud Publica. 2017;41:44.
27. Milanez H. Syphilis in Pregnancy and Congenital Syphilis: Why Can We not yet Face This Problem? Rev Bras Ginecol Obstet. 2016;38:425-27. http://dx.doi.org/10.1055/s-0036-1593603
28. Serruya SJ, Duran P, Martinez G, Romero M, Caffe S, Alonso M, et al. Maternal and congenital syphilis in selected Latin America and Caribbean countries: a multi-country analysis using data from the Perinatal Information System. Sex Health. 2015;12(2):164-9. http://dx.doi.org/10.1071/SH14191
29. Figueiró-Filho EA, Freire SSA, Souza BA, Aguena GS, Maedo CM. Sífilis e Gestação: Estudo Comparativo de Dois Períodos (2006 e 2011) em População de Puérperas. J Bras Doenças Sex Transm. 2012;24(1):32-7. http://dx.doi.org/10.5533/2177-8264-201224109
30. Cerqueira LRP, Monteiro DLM, Taquette SR, Rodrigues NCP, Trajano AJB, Souza FM, et al. The magnitude of syphilis: from prevalence to vertical transmission. Rev Inst Med Trop São Paulo. 2017;59:e78. http://dx.doi.org/10.1590/S1678-9946201759078
31. Holzmann APF, Silva CSO, Barros SMO, Barbosa DA. Assistência hospitalar a recém-nascidos expostos à transmissão vertical da sífilis. J Bras Doenças Sex Transm. 2017;29(Suppl. 1):3.
32. Silvestre MGP, Sortica AC, Leon JS, Fitz MRMS, Oliveira TH. Cobertura dos exames de HIV e sífilis em gestantes: a situação nos partos e abortamentos na rede privada do Rio Grande do Sul. DST J Bras Doenças Sex Transm. 2017;29(Suppl. 1):6.
33. Campos ACC, Arze WNC, Rodolfo LZ, Matos Neto OR, Villamizar HMM, Assis JM. Análise dos casos de notificação de sífilis congênita do município de Foz de Iguaçu – Paraná 2007-2016. DST - J Bras Doenças Sex Transm 2017;29(Supl. 1):13.
34. Santos VN, Xavier E, Timbó M, Fontes R, Silva PM, Travassos AG. Epidemiological panorama of gestational and congenital syphilis in the state of Bahia, Brazil. DST J Bras Doenças Sex Transm. 2017;29(Suppl. 1):14.
35. Gonçalves MVR, Benzaken AS, Kolling AF, Freitas FLS. Experiências exitosas para redução da sífilis congênita e as estratégias de "boas práticas" para administração de penicilina em quatro municípios do Brasil. DST - J Bras Doenças Sex Transm. 2017;29(Suppl. 1):28.
36. Pinto M, Borges V, Antelo M, Pinheiro M, Nunes A, Azevedo J, et al. Genome-scale analysis of the non-cultivable *Treponema pallidum* reveals extensive within-patient genetic variation. Nat Microbiol. 2016;2:16190. http://dx.doi.org/10.1038/nmicrobiol.2016.190
37. Arora N, Schuenemann VJ, Jäger G, Peltzer A, Seitz A, Herbig A, et al. Origin of modern syphilis and emergence of a pandemic *Treponema pallidum* cluster. Nat Microbiol. 2016;2:16245. https://doi.org/10.1038/nmicrobiol.2016.245
38. Lithgow KV, Hof R, Wetherell C, Phillips D, Houston S, Cameron CE. A defined syphilis vaccine candidate inhibits dissemination of *Treponema pallidum* subspecies pallidum. Nat Commun. 2017;8:14273. https://doi.org/10.1038/ncomms14273
39. Passos MRL, Nahn Junior EP, Almeida Filho GL, Godefroy P. Sífilis adquirida. In: Passos MRL, ed. Sífilis adquirida in Passos MRL. Deessetologia, DST 5. Rio de Janeiro: Cultura Médica; 2005.
40. Center for Diseases Control and Treantment. U.S. Public Health Service Syphilis Study at Tuskegee. The Tuskegee Timeline [Internet]. 2015 [cited on Feb 12, 2018]. Available at: https://www.cdc.gov/tuskegee/timeline.htm
41. Feldshuh D. Miss Evers' Boys. New York: Dramatic Plays Inc; 1988.
42. Sargen J. Miss Evers' Boys. Time Warner Entertaiment; 2001.
43. Takahashi T, Arima Y, Yamagishi T, Nishiki S, Kanai M, Ishikane M, et al. Rapid Increase in Reports of Syphilis Associated With Men Who Have Sex With Women and Women Who Have Sex With Men, Japan, 2012 to 2016. Sex Transm Dis. 2018;45(3):139-43. https://dx.doi.org/10.1097%2FOLQ.0000000000000768