Zika and Microcephaly: can we learn from history?

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Comentário

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Brazil is facing an epidemic of a severe birth defect: microcephaly, a condition linked with acute neurological impairments and developmental delays. Not all the children born with an abnormally small circumference of the head suffer from these problems, but many do (ASHWAL et al., 2009). The microcephaly epidemic is linked to infection by the zika virus, transmitted via the mosquito *Aedes aegypti*.[1] The latest epidemiological bulletin of the Brazilian Ministry of Health, of January 20, 2016, has reported 3,893 suspected cases – as compared with the 739 cases reported in the first epidemiological bulletin of 21 November 2015.[2] The majority of the cases of microcephaly have been observed in the North East of Brazil, especially in the states of Pernambuco, Paraiba and Bahia.

A baby born at full term with a head circumference of 32 cm or less (according to some experts, 33 cm or less) is defined as microcephalic. This is, however, a partly arbitrary definition. Some of the babies with a borderline head circumference (31-33 cm) will develop quasi-normally, while others will be seriously affected. Only time can tell whether a child with an intermediary head size will be affected or not. The Brazilian ministry of Health has declared the microcephaly outbreak a sanitary emergency and advised women in the most affected regions to postpone pregnancies. At the end of November the ministry also declared that the link between microcephaly and infection with the zika virus, first suspected on the basis of epidemiological data (a geographic correlation between the presence of zika infection and the appearance of microcephaly), and women's self-reported data (the zika virus often produces a typical rash in infected people), was confirmed through direct observation of the virus in affected newborns. Brazilian virologists and infectologists became persuaded in

DOI: http://dx.doi.org/10.1590/S0103-73312016000100002

late November 2015 that zika infection is – either alone or with other cofactor(s) – responsible for brain anomalies in newborns (PAHO, 2015). Epidemiologists also noted that in November and December 2015, the great majority of microcephaly cases were observed in poor women (TRIUNFOL, 2015).

Today there is no simple serum test able to detect anti-zika antibodies in the blood (this is the usual method to learn whether a given person is infected by a bacteria or virus), because antibodies against zika cross react with antibodies against dengue fever, yellow fever and chikungunya. Infection with zika has to be confirmed by virologists who look for the presence of the virus using reverse transcription – polymerase chain reaction (RT-PCR). The Health Ministry has instructed hospitals with microcephaly cases to send samples of blood from newborns diagnosed with this condition, together with samples of placenta tissue (if available) and maternal blood to a virology laboratory. In mid-December 2015, researchers found proof of zika infection in 134 cases of microcephaly.[3] The Health Ministry's instructions discuss only postnatal diagnosis of zika infection in affected children; they do not mention prenatal diagnosis of microcephaly or detection of maternal and fetal infection with zika.[4] By contrast, the US Center for Disease Control issued a detailed instruction for prenatal diagnosis of zika and zika induced fetal anomalies (PETERSEN et al., 2016).

Prenatal diagnosis of microcephaly is not easy. It is possible to detect abnormally small head size by obstetrical ultrasound, but it can be done only late in pregnancy, and the diagnosis is not fully reliable, especially in a heterogeneous populations such as the Brazilian one (BROMLEY; BENACERRAF, 2003). Moreover, the zika virus can attack the fetal brain without producing a large decrease in the head's size. Fetal medicine experts can detect brain lesion (intracranial calcifications), but again, this is feasible only the in late second and third trimester of pregnancy. The detection of zika infection in a pregnant woman may be more straightforward. When a women who lives in an affected region contracts a suspicious fever, especially if it is accompanied by a typical rash, a virology laboratory can verify whether she was infected with the zika virus and, if that is the case, perform an amniocentesis to check whether the fetus is infected too. This approach may, however, miss many cases of infection with zika, because on estimate that 80% of people infected with zika do not display typical symptoms of this disease. It is not clear whether asymptomatic

infection produced fetal anomalies. If scientists elaborate an inexpensive and reliable serological test for zika, it will be possible to propose such a test to all pregnant women and identify all those at risk of giving birth to an impaired child.[5] The question is, however, what will be the goal of such generalized testing. Finding out that a pregnant woman has contracted zika and confirming that the fetus is infected too, is pointless. There is no treatment which can prevent an abnormal development of the fetal brain, and a pregnant woman cannot elect to interrupt the pregnancy.[6]

The Brazilian government is focusing its efforts to stop the microcephaly epidemics on the fight against the spread of the zika virus, undoubtedly an important goal. Public health experts know, however, that this is not a simple task. The two actions that can halt the propagation of this virus – the elimination of its vector, the mosquito *Aedes aegypti*, and development of an anti-zika vaccine – are both complex endeavors. It is impossible to predict how much time will be needed to produce an effective anti-zika vaccine, as the difficulty of manufacturing an anti-HIV vaccine shows. It is also impossible to predict how rapidly *Aedes* can be eliminated from the affected regions, and whether such elimination will be sufficient to permanently remove the zika threat, as the difficulty of controlling dengue fever attests. In the meantime, specialists such as the virologist Pedro Vasconcelos, and the pediatrician Maria Angela Rocha, have expressed their hopelessness and feeling of impotence. As Dr. Vaconcelos put it, "we have our feet and hands tied down." (COSTA, 2015b; AZEVEDO, 2015). But how accurate is this statement? Are despair and inaction the only possible answer to a mounting number of children born with severe neurological impairment in Brazil?

This text examines an important historical precedent: physicians' reaction to infection with rubella (German measles). Women infected with the rubella virus in the first trimester of pregnancy are at high risk of giving birth to a child with severe fetal malformations. The rubella virus attacks the fetal central neural system and can induce numerous fetal malformations: blindness, deafness (and not infrequently, the combination of both), neurological problems and microcephaly.[7] It is impossible to predict the extent of such malformations. Some children born to infected mothers are healthy, some have sensory impairment(s) but no additional health problems, and some have severe neurological and cognitive problems.

Many women who contracted rubella early in pregnancy, and were aware of links between this disease and inborn malformations, wanted to have an abortion. In the 1940s, 50s and 60s, abortion was criminalized in Western Europe. Doctors who performed abortions risked prison and the loss of their medical license. In spite of the existence of such a legal context, numerous British and French doctors provided abortions to pregnant women infected with rubella. The great majority of such abortions were performed in public hospitals and clinics by physicians who believed that the considerable risk of severe inborn impairment, coupled with pregnant women's anguish, justified the bending of legal restrictions.[8]

Physicians knew, from the 19th century on, that "heredosyphilis" induced severe malformation of the newborn child. However, until the 1940s they were not aware of the fact that other maternal infections, including some which looked perfectly benign, could also induce fetal malformations. Rubella was the first virus connected with inborn impairments. In 1941, an Australian ophthalmologist, Norman Gregg, observed a link between congenital blindness and infection by the rubella virus during pregnancy.[9] Gregg's observations were rapidly confirmed and extended by other physicians. In 1947 the US pediatrician, Douglas Murphy, author of an influential textbook – *Congenital Malformations* – argued that women infected with the rubella virus early in pregnancy should be entitled to a legal termination of the pregnancy (MURPHY, 1947). Many doctors, especially in Europe, adopted this point of view.

Physicians had estimated that infection with the rubella virus produced major fetal malformation in 10 to 20% percent of the affected pregnant women, and probably an early pregnancy loss in many others.[10] Some physicians believed that such a risk was not sufficient to justify an abortion, since in most cases the woman would abort a healthy fetus. Others held the opposite opinion. Heated debates among specialists had, however, limited practical consequences. In the 1950s and 60s, British and French women who were infected with rubella early in pregnancy, were aware of the risk of fetal malformations, and wished to have an abortion, were nearly always able to find a practitioner who would perform this act, either in a private practice, or, in the majority of the cases, in a public institution (COVENTRY, 2000; VILLE; LOTTE, 2013).

In her widely debated paper on rubella and abortion of 1959, the British pioneer of medical genetics, Julia Bell, from the Galton Laboratory, University

College, London, stated that "now the facts of the situation have accumulated so that one can state without doubt that rubella in the early weeks of pregnancy is such a menace to the normal development of the fetus that it constitutes a risk one cannot allow to be taken for the unborn child." (BELL, 1959b, p. 686)[11] Answering her critics, Bell added that the problem of birth defects induced by infection with the rubella virus are at the same time individual and collective: "there are three main aspects of this problem, concerned with (a) the risks of severe handicap to the unborn child, (b) the risks of acute distress and difficulty for the potential parent, perhaps for the rest of her life, (c) the burden likely to rest upon the Welfare State. I appreciate the difficulty in reaching a decision in certain cases, but these must be very rare and do not touch the main problem." (BELL, 1959b, p. 686). Abortion, Bell explained in 1959 – that is, ten years before the decriminalization of abortion in the UK – has become the generally recognized treatment for the risk of fetal malformation induced by infection with the rubella virus: "to such an extent has this become routine treatment that maybe we can no longer hope to get measure of the risk involved or discover what proportion of such occurrences can be expected to result in a normally developed child." (BELL, 1959b, p. 686).

In 1961-1962, the Thalidomide scandal—an epidemic of fetal malformations produced by a popular tranquilizer, Thalidomide (Kevaldon), increased the public's awareness of environmental causes of birth defects.[12] The visibility of the Thalidomide scandal heightened women's fears of fetal malformations, and the scandal was immediately followed (1962-1964) by an epidemic of rubella in Europe and the US. At that time, doctors were able to confirm the infection of a pregnant woman with the rubella virus by measuring the rise in the anti-rubella antibodies in her blood. The availability of a serological test increased pressure on doctors to provide abortions to affected women who did not wish to continue their pregnancy.[13] Under the double pressure of the Thalidomide scandal and the rubella epidemic, abortion for risk of fetal malformation became increasingly perceived by the professionals and the general public as an acceptable way of managing such a risk (LOWY, 2014; REAGAN, 2010; COVENTRY, 2000).

As of January 2016, experts lack data about the precise consequences of infection with the zika virus during pregnancy. Such infection may be dangerous only in early stages of pregnancy, or it may be dangerous at any time during

the pregnancy; it may produce fetal malformations in a small proportion of infected women, or in a significant proportion of these women; the induction of fetal malformation by the zika virus may or may not be linked with the presence of additional factors. Research on this subject is urgently needed, as is the fight against the spread of the zika virus and efforts to produce a vaccine. On the other hand, a sanitary emergency is already present, and it seems well established that the zika virus is either the cause or an important cofactor in the microcephaly epidemics. It is not illogical to propose that, given the present state of knowledge, women infected with this virus while pregnant should be given the possibility to choose to terminate the pregnancy, especially when it is confirmed that the fetus is infected too.

In the middle of the 20th century, experts who argued that women contracting rubella early in pregnancy should be allowed to elect an abortion, spoke about the risk of suffering for the child and the family, not about the certainty of such suffering. People with severe impairments can live happy and fulfilling lives, and their families do not need to face distress, and can find deep satisfaction and joy in raising their child, especially if they receive adequate support from the society in which they live. Nevertheless, Julia Bell's concern that the birth of a severely impaired child may be a source of distress and difficulty for the child's mother, is no less valid today than it was in 1959. Only a pregnant woman, Bell and her colleagues believed, can decide whether she is ready and capable to take care of a special needs child, not infrequently as long as she lives. Brazilian women are not legally entitled to take such a decision, and in practice, in this domain like in many others, poor women have more limited choices than affluent ones.

In the meantime the number of newborns born with microcephaly continues to increase. The epidemic of neurological impairments, some experts fear, may be more severe than presently estimated, based exclusively on measures of the circumference of the newborns' cranium. Maria Angela Rocha explains that children born with a cranial perimeter of 32 cm and less usually have brain lesions visible on computerized tomography scans, while those born with a cranial perimeter of 33 cm and more usually do not have such lesions. This is not, however, an absolute rule. Some children with a cranial perimeter of 33 cm have detectable brain lesions, and children without visible lesions can develop

neurological problems (COSTA, 2015; AZEVEDO, 2015). The fetal medicine expert, Thomaz Gollop, from USP, similarly argues that a viral infection of the fetal brain can induce neurological and developmental difficulties in children born with a normal size head. To limit the microcephaly epidemic, Dr. Gollop proposes, women should delay pregnancies, and those already pregnant should avoid contact with mosquitos. Lower class women, he recognizes however, may have more difficulty adopting these precautionary measures. They have a more limited access to reliable contraception, and often live in areas infested by *aegypti* mosquitos (COLLUCI, 2015).

Microcephaly is scary. Pregnant women in rural Pernambuco report that they are terrorized by what they know about the zika epidemic and its consequences (COSTA, 2015a).[14] Brazilian doctors have no answer to their fears. Public health experts, such as the director of Fiocruz of Mato Grosso do Sul, Rivaldo Venâncio, predicts 15,000 cases of microcephaly—and possibly up to 50,000 zika-induced inborn anomalies – before the end of 2016 (MENDONÇA, 2016). When asked about the possibility that women will be allowed to abort a fetus at risk of microcephaly, Thomaz Gollop, like other Brazilian experts, has a single answer: "abortion is a crime" (COLLUCI, 2015).[15] Asked to provide information about the zika virus and microcephaly, Brazilian experts discuss only actions that can alleviate the symptoms of affected babies: convulsions, respiratory problems, difficulty of swallowing, developmental delays (BRASIL/MS, 2016).[16] In another time and place, physicians who, like their Brazilian colleagues today, worked in countries that criminalized abortion, had a different attitude towards women's plight. There is widespread agreement, the British obstetrician Bevis Brock of St. Bartholomew's Hospital, London explained in 1959, that, "when a pregnant mother, having had rubella, is aware of the risks and is prepared to face them, then no one would try to persuade her to accept termination. But if she feels unable to face the appalling anxiety of a pregnancy overshadowed by fear of a blind or deaf child, then it requires strong convictions to refuse this request" (BROCK, 1959).

Does Brazilian doctors' reluctance to consider interventions beyond the strict limits of legality reflect such strong convictions, or is it (also) affected by the fact that most women at high risk of giving birth to children with microcephaly and other zika-induced birth defects live in poor, often neglected areas?

References

ASHWAL, S. et al. Practice Parameter. Evaluation of the child with microcephaly (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society, *Neurology*, v. 73, p. 887-896, 2009.

AUBRY, M. C.; AUBRY, J. P.; DOMMERGUES, M. Sonographic prenatal diagnosis of central nervous system abnormalities. *Childs Nervous System*, v. 19, p. 391-402, 2003.

AZEVEDO, A. L. Entrevista com Pedro Vasconcelos: estamos com os pés e mãos atados. *O Globo*, 5 dec. 2015. Available at: <http://oglobo.globo.com/sociedade/saude/estamos-com-os-pes-maos-atados-diz-medico-sobre-zika-18227041>.

BELL, J. Correspondance. *British Medical Journal*, v. 1, n. 5132, p. 1302, 1959a.

_____. On rubella in pregnancy. *British Medical Journal*, v. 1, n. 5123, p. 686-688, 1959b.

BRASIL. Ministério da Saúde. Portal Saúde. *Informe epidemiologico* nº 04/2015. Available at: http://portalsaude.saude.gov.br/images/pdf/2015/dezembro/15/COES-Microcefalias---Informe-Epidemiol--gico---SE-49---15dez2015---10h.pdf>.

_____. Ministério da Saúde. Portal Saúde. Especialistas tiram dúvidas sobre zika e microcefalia. *Portal da saude*, 18 Jan. 2016. Available at: <http://www.brasil.gov.br/saude/2016/01/especialistas-tiram-duvidas-sobre-zika-e-microcefalia>.

BROCK, B. Rubella in pregnancy. *British Medical Journal*, v. 1, n. 5129, p. 1117, 1959.

BROMLEY, B.; BENACERRAF, B. Difficulties in the prenatal diagnosis of microcephaly. *Journal of Ultrasound in Medicine*, v. 14, n.4, p. 303-306, 1995.

COLLUCI, C. Alta de microcefalia reacende debate sobre aborto legal. *Folha de São Paulo*, 10 jan. 2016.

COLLUCI, C. "Melhor prevenção à microcefalia é evitar engravidar", afirma obstetra. *Folha de Sao Paolo*, 1 Dec. 2015. Available at: <http://www1.folha.uol.com.br/cotidiano/2015/12/1713277-melhor-prevencao-a-microcefalia-e-evitar-engravidar-afirma-obstetra.shtml>

COSTA, C. *BBC Brazil,* 15 Dec. 2015a. Microcefalia: Mães no sertão vivem angústia de não ter diagnóstico definitivo. Available at: <http://www.bbc.com/portuguese/noticias/2015/12/151214_maes_itapetim_cc>.

_____. Infectologista relata choque e desespero ao se deparar com início de epidemia de microcefalia. *BBC, São Paulo*, 30 nov. 2015b. Interview with the pediatrician Maria Angela Rocha, from Oswaldo Cruz Hospital, Recife. Available at: http://www.bbc.com/portuguese/noticias/2015/11/151127_depoimento_medica_microcefalia_cc.

COVENTRY, P. *The dynamics of medical genetics:* the development and articulation of clinical and technical services under the NHS, especially at Manchester c. 1945-1979. PhD thesis (History of Science) - Manchester University, Manchester, 2000.

DALLY, A. Thalidomide: Was the tragedy preventable'. *The Lancet*, v. 351, p. 1197-1199, 1998.

GREGG, N.A. Congenital cataract following German measles in the mother. *Transactions of the Ophthalmological Society of Australia*, v. 3, p. 35-46, 1941.

LOWY, I. Prenatal diagnosis: The irresistible rise of the «visible fœtus». *Studies in History and Philosophy of Biological and Biomedical Sciences*, v. 47, p. 290-299, 2014.

MAMMERI, Q.; FILLION, E.; CHEMPENOIS, B. Le juge et le diagnostique prenatal depuis la loi de 4 mars 2002. *Alter, European Journal of Disabiity Research*, v. 9, p. 331-353, 2015.

MCBRIDE, W. G. Thalidomide and congenital abnormalities. *The Lancet*, v. 278, p. 1358, 1961.

MENDONÇA, M. O zika hoje, depois da violência, é talvez um dos mais graves problemas de saúde pública no Brasil. Interview with the infectiologist and the director of Fiocruz do Mato Grosso do Sul, Rivaldo Venâncio, *Gazeta On Line*, 03/01/2016. Available at: <http://www.gazetaonline.com.br/_conteudo/2016/01/noticias/cidades/3919597-o-zika-hoje-depois-da-violencia-e-talvez-um-dos-mais-graves-problemas-de-saude-publica-no-brasil.html>.

MURPHY, D. P. *Congenital Malformations. A study of parental characteristics with a specific reference to the reproductive process.* Philadelphia: J.B. Lippincott Company, 1947 (2nd ed.), p. 106.

MUSSO, D. Zika virus transmission from French Polynesia to Brazil. *Emerging Infectious Diseases*, v. 21, n. 10, Oct., 2015. Available at: <www.cdc.gov/eid>.

NEVA, F.; ALFORD, C.; WELLER, T. Emerging perspectives on rubella. *Bacteriological Review*, v. 28 n. 4, p. 444-451, 1964.

PANAMERICAN HEALTH ORGANIZATION. Neurological syndrome, congenital malformations, and Zika virus infection. Implications for public health in the Americas. *PAHO Epidemiological Alert*, 1 December 2015.

PETERSEN, E. et al. Interim guidelines for pregnant women during a zika virus outbreak-United States, 2016. *CDC - Morbidity and Mortality Weekly Report*, 19 jan. 2016.

REAGAN, L. J. *Dangerous Pregnancies*: *Mothers, Disabilities and Abortion in Modern America.* Berkeley*:* University of California Press, 2010.

SHERIDAN, M. Final report of a prospective study of children whose mothers had rubella in early pregancy' *British Medical Journal*, v. 2, n. 5408, p. 536-539, 1964.

SUNDAY TIMES INSIGHT TEAM. *Suffer the Children:* the story of thalidomide. London: André Deutsch, 1979.

TRIUNFOL, M. A new mosquito-borne threat to pregnant women in Brazil. *The Lancet, Infectious Diseases*, 2015. Available at: <file://localhost/www.thelancet.com:infection>. Accessed: Dec. 23, 2015.

VILLE, I.; LOTTE, L. Évolution des politiques publiques: handicap, périnatalité, avortement. In: Final Report of the ANR project-09-SSOC-026 Les enjeux du diagnostic prénatal dans la prévention des handicaps: l'usage des techniques entre progrès scientifiques et action publique. Paris, 2013.

Notes

[1] The Zika virus, which belongs to the same family (flavivirus) as the dengue and chikungunya viruses, also transmitted by the mosquito *Aedes aegypti*, arrived in Brazil in the summer of 2014 (MUSSO, 2015). The zika virus was not linked earlier with birth defects. It is possible that it had undergone a mutation in Brazil**.**

[2] Available at: <http://g1.globo.com/bemestar/noticia/2016/01/casos-suspeitos-de-microcefalia-associada-ao-zika-chegam-3893.html>.

[3] They failed to find such evidence in 102 cases; the status of other cases was unknown, probably because of the absence of biological material that could be tested (BRASIL/MS, 2015).

[4] Brasil tem 2.165 casos suspeitos de microcefalia e 134 confirmados. *Valor Economico,* Dec., 15, 2015. Available at: <http://www.valor.com.br/brasil/4358602/brasil-tem-2165-casos-suspeitos-de--microcefalia-e-134-confirmados>.

[5] Alternatively, theoretically at least, it should be possible to extend virological testing to all pregnant women in the affected areas by scaling up the testing capacity of virology laboratories.

[6] The molecular biologist Alysson Muotri proposed, in his post on *Globo* of 16 Dec. 2015, to seek ways to prevent brain impairment in fetuses infected by Zika by manipulating the woman's immune system, because , he explained, this would be a more effective approach than fighting the epidemic through elimination of mosquitos, a strategy that has failed in Brazil in the past. Available at: <http://g1.globo.com/ciencia-e-saude/blog/espiral/post/o-zika-virus-e-microcefalia.html>.

[7] Microcephaly can be also induced by infection of a fetus with cytomegalovirus, herpes simplex virus, varicella virus and the parasite *Toxoplasma gondii*, the etiological agent of toxoplasmosis. It can be produced by toxic agents such as alcohol. Microcephaly is one of the manifestations of fetal alcohol syndrome.

[8] On the attitude of UK doctors, see Coventry (2000) and Ville & Lotte (2013).

[9] The first report on the link between rubella and birth defects was made by an Australian pediatric ophthalmologist, Norman MacAlister Gregg, in 1941 (GREGG, 1941). On the history of rubella epidemics and its role in the abortion debate see Reagan (2010).

[10] Ten to 20% was an average estimate. Some physicians believed that the proportion of affected fetuses was higher, and others believed it was lower (SHERIDAN, 1964; NEVA; ALFORD; WELLER, 1964).

[11] Julia Bell, who wrote this paper at the age of 80, had a long career as one of the pioneers of human genetics in the UK. Among others, she collaborated with J.B.S. Haldane on linkage studies in the 1930s, and in 1943 was co-discoverer, with J. Martin, of the fragile X syndrome.

[12] The first description of the link between thalidomide and birth defects was made by the Australian physcian Willliam McBride (McBRIDE, 1961). On the history of the thalidomide scandal, see Sunday Times Insight Team (1979) and Dally (1998).

[13] Such a diagnosis was difficult in the 1980s too. The most famous French case of 'harm from being born' – the Perruche verdict of 2000 – was a ruling in favor of a mother who was mistakenly informed in 1982 that she did not have rubella in early pregnancy, and then gave birth to a severely handicapped child (MAMMERI; FILLION; CHEMPENOIS, 2015).

[14] See also photoreportage «Geração microcefalia: histórias do surto que assusta o Brasil», *BOL/ photos,* 7 Dec. 2015, Available at: <http://noticias.bol.uol.com.br/fotos/imagens-do-dia/2015/12/07/geracao-microcefalia.htm#fotoNav=5>.

[15] Gollop, who supports abortion rights, added that in the present political climate there is practically no chance of a change in attitude to abortion for a non-lethal malformation.

[16] A few Brazilian gynecologists testified anonymously that they performed abortions when the fetus had showed signs of severe brain anomaly (COLLUCI, 2016).