British Journal of Medicine & Medical Research
4(32): 5107-5115, 2014

SCIENCEDOMAIN *international*
www.sciencedomain.org

Low and Zero Prevalence Rates of Anti-measles Virus Immunoglobulin G in Mothers and Their Infants Respectively in Health Centers in Osogbo, Nigeria

Oluwatoyin Adebusola Adegboye[1], Adetayo Abosede Adegboye[1], Moses Olubusuyi Adewumi[2] and Waidi Folorunso Sule[1*]

[1]Department of Biological Sciences, Faculty of Basic and Applied Sciences, Osun State University, PMB 4494, Oke-Baale, Osogbo, 230212, Osun State, Nigeria.
[2]Department of Virology, College of Medicine, University College Hospital, University of Ibaban, Ibadan, Nigeria.

Authors' contributions

Authors MOA and WFS conceptualized, formulated and addressed the research question/objective of the study. Authors OAA and AAA collected the blood samples. Author MOA (with authors OAA and AAA) completed the sample preparation and laboratory analysis. Author WFS organized the data/result and wrote the manuscript. All authors read and approved of the manuscript before sending to the Journal for publication.

Short Research Article

Received 25th February 2014
Accepted 6th May 2014
Published 10th July 2014

ABSTRACT

Aim: We undertook this study to determine the susceptibility of mother-infant pair participants to measles virus infection in two health centers in Osogbo, Osun State, Nigeria.
Study Design: This is a descriptive, cross-sectional hospital-based study.
Place and Duration of the Study: The study was carried out in Osogbo, southwestern, Nigeria between November, 2012 and February, 2013.
Methodology: With ethical approval and participants' consents, 83 mothers and their 84 infants were consecutively recruited; blood samples were aseptically collected from them by thumb puncture onto Whatman filter paper. The papers were appropriately labeled; air-dried and kept in brown envelopes which we kept in clean polythene bags and stored at 4ºC until assayed. Freshly prepared PBS was used to elute serum from 5 to 6

**Corresponding author: Email: waidifolorunso@uniosun.edu.ng, equine318@yahoo.com;*

punched-out disks from each Whatman filter paper. The supernatant from the spun eluate of each sample was assayed for anti-measles virus IgG using ELISA.
Results: Overall, 2.41% and zero percent seroprevalence rates were recorded from the nursing mothers and their infants respectively.
Conclusion: We concluded that the seropositivity of anti-measles virus IgG antibody in the nursing mothers from the two health facilities was very low, and that all the infants and most (97.59%) of the nursing mothers were apparently susceptible to measles virus infection.

Keywords: Measles IgG antibody; mothers; infants; susceptibility; Osogbo.

1. INTRODUCTION

Measles, a vaccine-preventable acute disease [1] caused by measles virus, is primarily a childhood disease that is highly contagious with high morbidity, disability and mortality; consequently it has been slated for eradication [2-8]. Measles is usually characterized by fever of ≥38ºC; maculopapular rash of about 3 days or more; with one or a combination of coryza, cough, conjunctivitis and Koplik's spots in the oral mucosa of measles infected individuals [2]. The virus is spread through contact with fluids from an infected person's nose and mouth, either directly or through aerosol transmission. A study conducted by Onoja et al. [9] in Oni Memorial Children's Hospital, Ibadan, south-western Nigeria reported that measles was still a major childhood problem that caused high morbidity and mortality.

Of the antibodies produced in human body, IgG isotype is the only one that crosses the placenta in pregnant women to developing fetus' blood circulation; thereby conferring primary protection against infections in the early life of newborns [10]. Such passively acquired antibodies [11,12] from mothers herein referred to as maternal measles antibodies (MMA) are of specific health significance. Besides conferring primary protection against infections in early life of newborns [13,14], they have been reported to impact response of infants to vaccines. Specifically, maternal antibodies have been shown to inhibit seroconversion in infants following vaccination with hepatitis A virus [15], human para-influenza virus type 3 [16], rotavirus [17], tetanus [18] and some other vaccines.

The efficiency of trans-placental and amount of IgG transferred to fetus depend on several factors such as, total concentration of IgG in mother, the type of vaccine, the time between vaccination of the mother and delivery, the gestational age of the fetus at birth and the concentration of vaccine-specific IgG and IgG subclasses in mother [19,20]. Reports have also shown that modern-day mothers are more measles vaccine-immune contrary to natural measles virus-immune and as such, produce low titer anti-measles virus antibody which consequently decays or clears from their respective infants earlier than 9 months of age when measles vaccine is routinely administered in Nigeria, and other countries [11,21-23]. Earlier, Sato et al. [24] reported that the passively acquired anti-MV IgG (MMA) in neonates is subjected to an exponential clearance rate with a half-life of 35 to 40 days.

There is a dichotomy regarding this: firstly, when the MMA is absent or present below protective levels in neonates, such are susceptible to measles virus infection; secondly, when present at considerable titer, the MMA inhibits immune response to vaccine antigens following immunization. Therefore, it is only after MMA level is low enough, at about 6 to 9 months of age, that vaccine antigens (or virus) can be given to infants to induce effective

adaptive immunity [25]. The presence or absence of MMA in infants is therefore a factor to consider in immunization of infants against measles. In Nigeria the recommended age for routine MMR vaccination is 9 months [26], however, whether or not this is optimal remains a subject of debate.

Antibody and viral RNA are sufficiently stable on dried blood spot (DBS) at ≤98.6ºF(≤37.0ºC) to allow this sample collection method to be used for case confirmation or molecular epidemiology in areas where sample refrigeration is not feasible [27], therefore DBS has been used for various epidemiologic studies for the detection of measles- and rubella-specific IgG and IgM antibodies and viral RNA [28-30]. This study was hence designed to detect, using enzyme-linked immunosorbent assay (ELISA), the presence of anti-measles virus IgG antibody in nursing mothers and their infants presented for routine measles, mumps, rubella (MMR) immunization in two health centers in Osogbo. This is to enable us determine their susceptibility to measles virus infection.

2. MATERIALS AND METHODS

2.1 Study Area and Sample

The study was carried out between November, 2012 and February, 2013 in Osun State Specialist Hospital, Asubiaro (SSHA; N07.76439º; E004.54680º) and Primary Health Care Centre (PHCC, N07.77068º; E004.54807º), Odi-olowo, Osogbo, Osun State, Nigeria. The study participants were consenting apparently healthy mothers and their respective infants aged 9 months who were presented to the hospitals for measles immunization. The people of Osogbo, capital of Osun state, are predominantly Yorubas and other tribes from various parts of the country; as well as foreigners.

2.2 Study Design

This is a descriptive, cross-sectional hospital-based study. The study was designed to detect anti-measles virus IgG in nursing mothers and maternal anti-measles virus IgG in their nine-month old infants. The ethical approval to conduct the study was obtained from University of Ibadan-University College Hospital Ethical Review Board. The objectives of the study were explained to the Management of the health facilities. A medical personnel assigned by each of the hospitals discussed the objectives of the study with the nursing mothers. Thereafter, we consecutively selected 83 mothers who gave consents to participate in the study; however, the studied infants were 84 in number because a mother had a twin. Inclusion criteria were being a nursing mother of infants aged ≤9 months, presenting such infants for routine MMR immunization in the two study health centers; exclusion criteria included not being a nursing mother, nursing mother having infants older than 9 months, not presenting infants for routine MMR immunization even if the infants was ≤9 months in the two study health centers and refusal to participate.

2.3 Sample Collection and Storage

Blood sample was collected aseptically from each participant by thumb puncture using sterile lancets. The blood was collected by placing the underside of marked area of each Whatman filter paper number 3.0 on the bleeding spot; the papers were allowed to completely air-dry at ambient temperature, the papers were appropriately labeled [31-33]. With the dried blood spots on them, the Whatman filter papers were packed inside brown

envelopes, transported to Department of Virology, College of Medicine, University College Hospital, Ibadan. Subsequently, the envelopes were wrapped in polythene bags and stored at refrigerated temperature (4ºC) until used for serology.

2.4 Serum Extraction from Whatman Papers

With 70% alcohol-sterilized metal paper hole-punch, DBS disks (about 6mm diameter each) were punched out from each Whatman paper into appropriately labeled plain blood sample tube. The metal hole-punch was wiped with 70% alcohol before re-use to punch out disks from another Whatman paper. Only the punched-out paper disks completely covered with blood were used for serum extraction. Five hundred microlitres of freshly prepared phosphate buffered saline solution was added to each of the plain tube containing 5-6 punched-out paper disks. The tubes were left overnight at ambient temperature to achieve serum elution. The following day, the eluate was spun at 2000rpm for 10 minutes and the supernatant from each sample served as the serum for ELISA.

2.5 Serological Analysis of the Serum Samples

The sera were qualitatively assayed for anti-measles virus IgG antibodies with commercial ELISA kit (Enzyme immunoassay for the semi-quantitative determination of IgG antibodies by Diagnostic Bioprobes, Milano-Italy). The ELISA was performed at the Department of Virology, College of Medicine, University College Hospital, Ibadan, Oyo state, Nigeria. The results were interpreted according to instructions of the kit's manufacturer.

2.6 Data Analysis

The data we generated were entered into Excel spread sheet for organization and analysis. The results were then presented with descriptive statistics; Microsoft Office Excel, 2007 version was used for data analysis.

3. RESULTS

Out of the 83 mothers (19-42 years; mean age 27.6 years), only 2 (2.41%) (one each from the two study centers) had detectable anti-measles virus IgG antibody. None of the 84 nine-month-old infants (42 each of females and males i.e. 1:1 female to male ratio) had detectable maternal measles IgG (Table 1).

Table 1. Maternal measles IgG antibody among mother-infant pairs in two health centers in Osogbo, southwestern, Nigeria

Locations	Nursing mothers			Infants		
	Number tested	Number positive	Prevalence rate (%)	Number tested	Number positive	Prevalence rate (%)
SSHA	18	1	5.56	18	0	0.0 (0.0)
PHCC	65	1	1.54	66	0	0.0 (0.0)
Total	83	2	2.41	84	0	0.0 (0.0)

4. DISCUSSION

Overall, 2 mothers (2.41%) had detectable anti-measles virus IgG antibody while none of the infants (0.00%) had detectable MMA in their blood samples. Since none of the infants had detectable maternal derived IgG, we imply thus: it is either the two nursing mothers with detectable antibody did not transfer anti-measles virus IgG antibody to their respective infants probably as a result of low titer IgG, or the MMA had decayed before we collected blood samples from the infants. A similar observation had been reported by Haruna et al. [34] in a University Teaching Hospital in Borno State, northeastern, Nigeria that 2 infants from mothers with measles virus-specific IgG did not acquire MMA; the study reported infants without MMA as susceptible to measles.

Another implication of our observations is that mothers (97.59%) without detectable anti-measles virus IgG antibody were susceptible to measles; if these were infected, they could infect their infants or other susceptible contacts.

A study in Antwerp, Belgium by Leuridan et al. [35] in which venous whole blood was used to determine IgG MMA using ELISA reported that at 6 months of age, more than 99% of infants of vaccinated women and 95% of infants of naturally immune women had lost maternal antibodies. The study concluded that such infants were susceptible to measles virus infection at early age. By implication therefore, all the infants tested in our study were, at the time of presentation for measles virus containing-vaccine, susceptible to measles.

Another study conducted (in University of Bern, Bern, Switzerland) at 9 to 12 months of age using anti-measles virus IgG ELISA, revealed that 53 of 58 (91.4%) infants had no detectable MMA [25]. No detectable MMA had also been observed in 36 of 51 (71%) 9-month old infants when anti-measles virus neutralization test was used [36].

Studies have shown that there is decrease of natural boosting effect of the wild-type measles virus [37] and that many nowadays mothers become immune through measles vaccination; also that measles vaccine induces lower antibody titers in mothers who consequently transferred low titer measles virus antibodies to their infants with resultant early loss of such usually before 6 to 9 months of age compared to natural measles immune-mothers and their infants [21,22,23,35].

We wish to report that presentation of the study infants at 9 month-old for measles immunization could be said to be appropriate for two reasons (1) there was no IgG MMA to inhibit their adaptive humoral immune response to measles virus antigen [38-40], and (2) they were at the study period susceptible to measles infection. But viewing the absence of MMA during the study period from another perspective of susceptibility, more so in case they had lost the MMA some months before, one might say the presentation of the infants for MMR at 9 month-old was inappropriately delayed; may be the infants should have been presented earlier to protect them against possible exposure to wild-type measles virus which, more often than not, results in high morbidity and mortality in non-immune children [41,42]. This is supported by report that due to the decreased maternal protection provided by vaccinated mothers, infants too young to get immunized are at increased risk [43].

Though the issue of whether or not the studied infants had protective anti-measles virus antibody did not arise as they had no detectable antibody at all. A study in Netherlands had shown that the estimated duration of protection by maternal antibodies among infants in the general population, most of who were born to vaccinated mothers, could be as short as 3.3

months for measles [44]. Another study by Kizito et al. [45] in Entebbe-Uganda reported that 25% of infants had no protective measles-specific IgG levels. The study further revealed that maternal malaria infection, infant malaria parasitaemia, infant HIV and infant wasting were the factors associated with reduced measles-specific antibody levels in infancy. A study conducted in France also showed that passively transferred maternal antibodies against measles decline rapidly during the infant's first months of life, to reach mean concentrations below the sero-protective level at 6 months of age. Reportedly, ninety per cent of infants are no longer protected against measles at 6 months of age which is consistent with observations in other countries, where populations were immunized routinely against measles [1,46].

This study could also not state whether or not the infants obtained MMA from their mothers and if they did, the precise time each one lost the MMA was not known because this is not a longitudinal study. Some studies have documented concordance and discordance in measles virus antibody in mother-infant pairs either by detection of neutralizing or hemagglutination-inhibition antibodies [47].

It is somewhat intriguing, though the study sample size was small, that infants from two different health centers in Osogbo had no detectable MMA. This calls for further studies to ascertain the actual age at which infants in Osogbo lose MMA which may necessitate a modification of 9 months age for routine MMR immunization in Osogbo and Nigeria as whole. This is necessary considering the infectiousness of wild-type measles virus and attendant morbidity and mortality that may occur in case a child is naturally infected with wild-type virus.

A limitation of the study is that we failed to collect other pertinent demographic data like educational level, marital status, place of residence, history of measles immunization or natural measles experience, standard of living *et cetera* of the mothers. Therefore, we could not determine possible factors that could have contributed to the zero MMA prevalence rate among the infants. Similarly, we could not ascertain whether or not the loss of MMA among the infants occurred before the study period.

5. CONCLUSION

We concluded that the seropositivity of anti-measles virus IgG antibody in the nursing mothers from the two health facilities was very low while those without the antibody were apparently susceptible to measles; and that two sero-discordant mother-infant pair for anti-measles virus IgG antibody were observed. The study infants from the two health facilities were all susceptible (100.0%) to measles virus infection. We recommend that nursing mothers and women of child-bearing age without detectable anti-measles virus IgG antibody be immunized with measles virus-containing vaccine. We also recommend a similar study in Osogbo in about 3 to 6 month-old infants using venous blood and/or DBS; in addition, nursing mothers should continue to present their infants for routine MMR immunization in Osogbo.

ACKNOWLEDGEMENTS

The authors acknowledge the permissions and supports of the Managements of the two health centers used for the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Gans HA, Maldonado YA. Loss of passively acquired maternal antibodies in highly vaccinated populations: An emerging need to define the ontogeny of infant immune responses. JID. 2013;208(1):1-3.
2. Takeuchi K, Takeda M, Miyajima N. Toward understanding the pathogenicity of wild-type measles virus by reverse genetics. JID. 2002;55:143-149.
3. Centers for Disease Control and Prevention (CDC). Update: Global measles control and mortality reduction worldwide, 1991-2001. MMWR. 2003;52:471-5.
4. Pan-American Health Organization. Measles Elimination, Field guide, Second Edition. Scientific and Technical Publication No. 605, Pan American Sanitary Bureau, Regional Office of the World Health Organization, 525 Twenty-third Street, N.W. Washington, D.C. 2003;7:2005.
5. WHO. Progress in reducing global measles deaths: 1999-2003. WHO WER. 2005;80:78-81.
6. Griffin DE. Measles virus. In: Knipe DM, Howley PM, editors. Fields Virology, 5th ed. Lippincott Williams & Wilkins; 2007.
7. Lamb RA, Parks GD. Paramyxoviridae: The Viruses and Their Replication. In: Knipe DM, Howley PM, editors. Fields Virology, 5th ed. Lippincott Williams & Wilkins; 2007.
8. World Health Organization. Measles: Mortality Reduction and Regional Elimination. Strategic plan 2001-2005. Available at: http://www.who.int/vaccines-documents/.
9. Onoja AB, Adeniji AJ, Faneye A. Measles complications in a Nigerian hospital setting. Clin Rev Opinions. 2013;5(2):18-23.
10. Zinkernagel RM. Advances in immunology: Maternal antibodies, childhood infections, and autoimmune diseases. N Engl J Med. 2001;345:1331-5.
11. Leuridan E, van Damme P. Passive transmission and persistence of naturally acquired or vaccine-induced maternal antibodies against measles in newborns. Vaccine. 2007;25(34):6296-304.
12. Ahmadu BU, Pwavimbo AJ, Ibrahim RA, Abdullahi IB, Hassan SI, Claphton DH. The impact of maternal socioeconomic class on maternal measles antibodies of mother-infant pairs at birth in a Nigerian city. BRJMCS. 2013;2(3):37-40.
13. Goncalves G, Nascimento MS, Reu C, Cutts FT. Levels of rubella antibody among vaccinated and unvaccinated Portuguese mothers and their newborns. Vaccine. 2006;24:7142–7.
14. Chan J, Nirwati H, Triasih R, et al. Maternal antibodies to rotavirus: Could they interfere with live rotavirus vaccines in developing countries? Vaccine. 2011;29:1242–7.
15. Balli F, Di Biase AR, Viola L. Vaccination against hepatitis A. Pediatr Med Chir. 1996;18:259-62.
16. Lee MS, Mendelman PM, Sangli C, Cho I, Mathie SL, August MJ. Half-life of human para-influenza virus type 3 (hPIV3) maternal antibodies and cumulative proportion of hPIV3 infection in young infants. J Infect Dis. 2001;183:1281-4.
17. Nguyen TV, Yuan L, Azevedo MS. High titers of circulating maternal antibodies suppress effector and memory B-cell responses induced by an attenuated rotavirus priming and rotavirus-like particle-immunostimulating complex boosting vaccine regimen. CVI. 2006;13:475-85.

18. Siegrist CA, Barrios C, Martinez X. Influence of maternal antibodies on vaccine responses: Inhibition of antibody but not T cell responses allows successful early prime boost strategies in mice. Eur J Immunol. 1998;28:4138-48.
19. Englund JA. The influence of maternal immunization on infant immune responses. J Comp Pathol. 2007;137(1):S16-S19.
20. Saji F, Samejima Y, Kamiura S, Koyama, M. Dynamics of immunoglobulin at the feto-maternal interface. Rev Reprod. 1999;4:81-9.
21. Leineweber B, Grote V, Schaad UB, Heininger U. Transplacentally acquired immunoglobulin G antibodies against measles, mumps, rubella and varicella-zoster virus in preterm and full term newborns. Pediatr Infect Dis J. 2004;23:361–3.
22. Wang Z, Zhang S, Luo C, et al. Transplacentally acquired maternal antibody against hepatitis B surface antigen in infants and its influence on the response to hepatitis B vaccine. PLoS One. 2011;6:e25130.
23. Hisano M, Yamaguchi K. Usefulness of influenza vaccination during pregnancy to mothers and young infants. Expert Rev Vaccines. 2012;11:903–5.
24. Sato H, Albrecht P, Reynolds DW, Stagno S, Ennis FA. Transfer of measles, mumps and rubella antibodies from mothers to infants. Its effect on measles, mumps and rubella immunization. Am J Dis Child. 1979;133:1240-3.
25. Nicoara C, Zach K, Trachsel D, Germann D, Matter L. Decay of passively acquired maternal antibodies against measles, mumps, and rubella viruses. Clin Diagn Lab Immunol. 1999;6(6):868–71.
26. Hartter HK, Oyedele OI, Dietz K, Kreis S, Hoffman JP, Muller CP. Placental transfer and decay of maternally acquired anti-measles antibodies in Nigerian children. Pediatr Infect Dis J. 2000;19(7):635-41.
27. CDC. Recommendations from an Ad Hoc Meeting of the WHO Measles and Rubella Laboratory Network (LabNet) on Use of Alternative Diagnostic Samples for Measles and Rubella Surveillance. MMWR. 2008;57(24):657-60.
28. Ibrahim SA, Abdallah A, Saleh EA, Osterhaus ADME, de Swart RL. Measles virus-specific antibody levels in Sudanese infants: A prospective study using filter-paper blood samples. Epidemiol Infect. 2006;134:79–85.
29. Riddell MA, Byrnes GB, Leydon JA, Kelly HA. Dried venous blood samples for the detection and quantification of measles IgG using a commercial enzyme immunoassay. Bull World Health Organ. 2003;81:10.
30. El Mubarak HS, Yüksel S, Mustafa OM, Ibrahim SA, Osterhaus AD, de Swart RL. Surveillance of measles in the Sudan using filter paper blood samples. J Med Virol. 2004;73:624-30.
31. Nakano JH, Miller DL, Foster SO, Brink EW. Microtiter determination of measles hemagglutination inhibition antibody with filter papers. J Clin Microbiol. 1983;17:860–3.
32. Riddell MA, Leydon JA, Catton MG, Kelly HA. Detection of measles virus-specific immunoglobulin M in dried venous blood samples by using a commercial enzyme immunoassay. J Clin Microbiol. 2002;40(1):5-9.
33. Uzicanin A, Lubega I, Nanuynja M, Mercader S, Rota P, Bellini W, Helfand R. Dried blood spots on filter paper as an alternative specimen for measles diagnostics: detection of measles immunoglobulin M antibody by a commercial enzyme immunoassay. J Infect Dis. 2011;204:S564–S69.
34. Haruna SB, BukBuk DN, Dawurung JS. Mother-to-child transfer of measles antibody among patients attending University of Maiduguri Teaching Hospital, Borno State, Nigeria. Researcher. 2010;2(8):36-42.
35. Leuridan E, Hens N, Hutse V, Ieven M, Aerts M, Van Damme P. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. BMJ. 2010;340:c1626.

36. Maldonado YA, Lawrence EC, DeHovitz R, Hartzell H, Albrecht P. Early loss of passive measles antibody in infants of mothers with vaccine-induced immunity. Pediatrics. 1995;96(3):447-50.
37. Maria M, Elena C, Vassiliki P. Reduced measles and varicella passive immunity and susceptible infants in the 21ST century. Myth or reality? AJBS. 2011;1(1):8-12.
38. Dagan R, Slater PE, Duvdevani P, Golubev N, Mendelson E. Decay of maternally derived measles antibody in a highly vaccinated population in southern Israel. Pediatr Infect Dis J. 1995;14:965-9.
39. Gans H, DeHovitz R, Forghani B, Beeler J, Maldonado Y, Arvin AM. Measles and mumps vaccination as a model to investigate the developing immune system: Passive and active immunity during the first year of life. Vaccine. 2003;21:3398-405.
40. Glezen WP. Effect of maternal antibodies on the infant immune response. Vaccine 2003;21(24):3389-92.
41. Oldstone MBA. Viruses, plagues, and history. New York, USA. Oxford University Press; 1998.
42. Hamidu JL, Salami HA, Ekanem AU, Hamman L. Prevalence of protein-energy malnutrition in Maiduguri, Nigeria. Afr J Biomed Res. 2003;6:123-7.
43. Maria M, Vassiliki P. Current Measles Outbreaks. Can We Do Better for Infants at Risk? Pediatr Infect Dis J. 2012;31(7):756-58.
44. Waaijenborg S, Hahné SJM, Mollema L, et al. Waning of Maternal Antibodies Against Measles, Mumps, Rubella, and Varicella in Communities with Contrasting Vaccination Coverage. JID. 2013;1-7.
45. Kizito D, Tweyongyere R, Namatovu A, et al. Factors affecting the infant antibody response to measles immunisation in Entebbe-Uganda. BMC Public Health. 2013;13:619.
46. Arnaud G, Didier P, Aubert M, et al. Kinetics of decline of maternal measles virus-neutralizing antibodies in sera of infants in France. Clin Vac Immunol. 2008;15:1845-50.
47. Kacica MA, Venezia RA, Miller J, Hughes PA, Lepow ML. Measles antibodies in women and infants in the vaccine era. J Med Virol. 1995;45:227–9.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=599&id=12&aid=5280