



The insignificance of MBL2 protein levels in conferring resistance to malaria infection in Uyo Metropolis, Akwa Ibom State, Nigeria

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Abstract

Mannose binding lectin (MBL2) is an innate immune system pattern recognition molecule that serves to identify pathogens through their surface antigen-pathogen associated molecular patterns and bind to particular sugar molecules on the surface of pathogens to activate their destruction by the immune system. The levels of the immune protein- mannose binding lectin- correlate with the resistance of an individual to disease infections. Samples for this study were recruited from the Uyo metropolis of Akwa Ibom State in Nigeria. The levels of MBL2 were measured by enzyme-linked immunosorbent assay in 60 malaria patients and 60 healthy individuals for determination of resistance or protection against malaria infection. MBL2 levels in malaria patients and healthy controls were $14.40\text{ng/ml} \pm 13.04$ and $19.90\text{ng/ml} \pm 18.52$, respectively. The results from the study showed that there was no association in MBL2 levels between malaria and controls ($p=0.129$) as well as between the different sub-groups. Therefore, levels of MBL2 are not a contributory factor in resistance against malaria in the population under study.

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1.0 Introduction

Despite the intense, positive-result-yielding malaria control and elimination effort of the World Health Organization, which saw the decline of malaria endemic countries from 108 to 84 in the last two decades, malaria has continued to be among the leading causes of death from infectious diseases, with Nigeria alone accounting for 31% of the 14.8 global malaria mortality rate (deaths per 100,000 population at risk) in 2021 (WHO, 2022a). The burden of malaria in the WHO African region and particularly Nigeria is attributable to the transmission of *Plasmodium falciparum* by *Anopheles gambiae* and a recently detected *Anopheles stephensi*, which is prevalent in urban areas and considered to pose an extra challenge to control measures due to its resistance to insecticides (Sinka *et al.*, 2020; WHO, 2019, 2022b). Therefore, high morbidity and mortality attributed to malaria, particularly among pregnant women and children under the age of five, remain sustained.

Considering vector and parasite resistances to control measures like insecticide-treated nets (ITNs) and artemisinin combined therapies (ACTs), respectively, the last resort for the control, elimination, or eradication of malaria is the development of a vaccine for the parasite (Crompton *et al.*, 2010). However, this venture is strongly hampered by the complex life cycle and ever evolving nature of the parasite (Florens *et al.*, 2002; Gardner *et al.*, 2002). The immediate goals of malaria vaccine research were to induce robust immune responses, identify protective antigens, and combine candidate immunogens successfully to elicit adaptive immunity. A major breakthrough in malaria vaccination came with the WHO's recommendation of RTS,S (Mosquirix™) vaccine. This vaccine which has a pre-erythrocytic activity for the vaccination of children in malaria endemic regions (Zavala, 2022) was assigned the name RTS, since it was obtained from a combination of the repeat (R) and T-cell epitope (T) of the pre-erythrocytic

circumsporozoite protein (CSP) of *Plasmodium falciparum* genes and a surface antigen (S) of the hepatitis B virus and additional hepatitis B surface antigen (S) (Egbewande, 2022). Intense effort has been made in this direction as several vaccine candidates, such as Blood Stage Vaccines (BSVs), Placental Malaria Vaccines (PMVs) and Transmission Blocking Vaccines (TBVs), have gone through several stages of development already (Duffy & Patrick Gorres, 2020).

Pivotal to the malaria vaccine development technology is the knowledge of the parasite surface molecules that play major roles in infection and susceptibility to infectious diseases (Macola & Fauci, 2020). These molecules encompass immunogens and surface proteins that the pathogens express, which aid in inducing immune responses against these invading pathogens. These molecules are recognized through their associated molecular patterns (PAMPs) by immune proteins. A typical immune protein that plays a key role in the recognition and initiation of immune activity against infectious pathogens is the mannose binding lectin.

Mannose binding lectin (MBL), also referred to as mannan-binding protein or core specific lectin (Turner, 1996), expressed by the human MBL gene –*MBL2* which is mapped to the human chromosome 10 (10q11.2-q21) (Sastry *et al.*, 1989) is an innate immune system pattern recognition molecule (PRM) that recognizes pathogens through their pathogen associated molecular patterns (PAMPs) and initiates, regulates, and amplifies innate immune response against such pathogens (Boldt *et al.*, 2006). The C-type liver serum (Eisen & Minchinton, 2003), acute phase protein (Ezekowitz *et al.*, 1991), is a 32 KDa polypeptide consisting of 248 amino acids with a cysteine-rich N-terminal, a collagen-like domain, a helical neck, and a C-terminal (Ezekowitz & Stahl, 1988) which is the recognition domain; hence, it is classified

among the collectin protein family (Auriti *et al.*, 2017).

MBL plays a vital role in innate immunity through specific binding to sugar moieties expressed on the surfaces of a variety of microorganisms (bacteria, viruses, fungi and parasites) thereby activating the lectin complement pathway and enhancing opsonophagocytosis (Ezekowitz *et al.*, 1989; Neth *et al.*, 2002; Neth *et al.*, 2000; Townsend *et al.*, 2001; Ying *et al.*, 2004). The mode of operation of the complement pathways at the different stages of the life cycle of the *Plasmodium falciparum* has been studied (Rathnayake *et al.*, 2021). In its action against invading microbes, including *P. falciparum*, MBL binds MBL-associated serine proteases such as MASP -1,-2 and -3 to initiate immune response through the activation and coordination of complement-mediated phagocytosis, membrane attack complex, and proinflammatory cytokines release (Garred *et al.*, 2003; Jack & Turner, 2003; Larsen *et al.*, 2004). Susceptibility or resistance to infectious diseases have been linked to MBL levels, particularly in children and in adults with underlying autoimmune deficiency diseases (Bağ-Romaniszyn *et al.*, 2020; Cosar *et al.*, 2008; Eisen & Minchinton, 2003; Garcia-Laorden *et al.*, 2006; Petersen *et al.*, 2001; Takahashi & Ezekowitz, 2005).

There is a differential expression of MBL among individuals and populations. This differences in MBL levels is as a result of structural (point) mutations at codon 52, 54 and 57 of exon 1 of the MBL-2 and promoter gene polymorphisms at the 5' flanking region of the MBL-2 at -550 and -221 positions (Lipscombe *et al.*, 1993; Minchinton *et al.*, 2002; Sumiya *et al.*, 1991). The point mutations, some of which are of high frequency in sub-Saharan Africa have been associated with low MBL levels particularly among individuals who are homozygous for the mutant allele; these individuals have been

observed to be of increased susceptibility to infectious diseases (Lambourne *et al.*, 2009; Luty *et al.*, 1998; Mombo *et al.*, 2003; Peterslund *et al.*, 2001; Shen *et al.*, 2020; Tong *et al.*, 2019).

Several association studies between MBL-2 variants/levels and clinical malaria presentations or other diseases have been conducted. However, the results of these studies are contradictory for different (African) populations: while some reported no associations, such as in tuberculosis (Udosen *et al.*, 2021), as well as in some polymorphisms of another immune protein, such as toll-like receptor 2 (Udosen, 2019 and Udosen 2020) majority concludes findings of association between the MBL and clinical malaria presentations (Bellamy *et al.*, 1998; Boldt *et al.*, 2009; Boldt *et al.*, 2006; Futagbi *et al.*, 2022; Garred *et al.*, 2003; Holmberg *et al.*, 2008; Luty *et al.*, 1998) and tuberculosis (Udosen and Nya, 2017). It is on the basis of this discrepancy that Denholm and Co-Workers(2010) suggested that the best approach to revealing the association between MBL deficiency and susceptibility to infections may be the direct assessment of the protein by measuring serum MBL levels in individuals. Moreover, despite a handful of studies on the association of MBL and malaria in African populations, to the best of our knowledge, there is no such study on a Nigerian population.

We therefore, set out to investigate the association between mannose binding lectin levels and malaria infection among individuals in the Uyo Metropolis of Akwa Ibom State, Nigeria, through a direct measurement of serum MBL levels among recruited subjects.

2.0 Materials and Methods

We recruited a total of 120 individuals from St. Luke's Hospital, Anua, Uyo, and the University of Uyo Teaching Hospital (UUTH), Uyo in line with the institution's Ethical Regulations. The

participants comprised 60 individuals who were diagnosed with symptomatic malaria as cases and 60 healthy individuals as controls. On a gender basis, the study population was made up of 21 males and 39 females for healthy controls, with 37 females and 23 males for malaria cases.

Laboratory analysis was carried out at UUTH medical laboratory. Ethical approval for the study was sought for and obtained from the hospitals study samples were gotten from. The blood samples were collected from cases and controls in accordance with ethical guidelines.

The presence of malaria parasites in samples was detected by microscopy using whole blood. To obtain serum/plasma for subsequent Enzyme-linked Immunosorbent Assay (ELISA) analysis, whole blood was centrifuged at 1500 rpm to obtain serum/plasma. Measurement of serum/plasma MBL2 concentrations was carried out by ELISA technique following

manufacturer's (OriGene Technologies) protocols. Final analysis was performed excluding samples with outlier values.

To determine the level of association of MBL2 concentrations with susceptibility to malaria, the data obtained was subjected to statistical analysis. The T-test and one way analysis of variance (ANOVA) were employed in assessing the level of association between groups, with the level of significance set at $p \leq 0.05$.

3.0 Results

The result of the assay indicated the mean MBL2 levels in malaria cases were 14.41 ± 13.04 ng/ml, while those of healthy subjects were 19.90 ± 18.52 ng/ml (Table 1). There was no significant difference between the MBL2 levels of malaria cases and healthy controls when the two groups were subjected to statistical testing ($p = 0.129$)

Table 1: Mean MBL2 levels of study subjects by gender

Population	Malaria Cases (ng/ml)	Healthy Controls (ng/ml)
Total Population	14.41 ± 13.04	19.90 ± 18.52
Male	16.98 ± 13.90	15.50 ± 15.90
Female	22.09 ± 15.20	20.90 ± 18.80

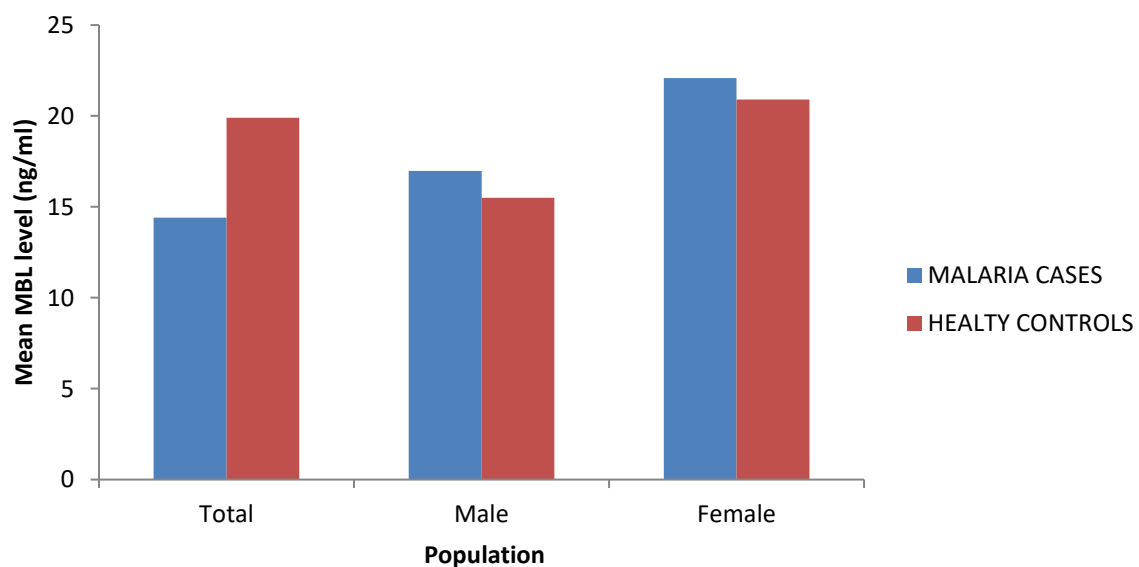


Fig.1: Mean MBL2 levels in malaria cases and healthy controls across study populations

Gender based analysis showed the mean MBL2 level for male malaria cases was 16.98 ± 13.90 ng/ml and that for male healthy controls to be 15.50 ± 15.90 ng/ml. The mean MBL2 levels for female malaria cases were 22.09 ± 15.20 ng/ml while those of female healthy controls were 20.90 ± 18.80 ng/ml. The MBL levels between male and female patients were not significantly different ($p = 0.458$).

Further stratification of the study population was based on age grouping. The mean MBL2 levels of the malaria cases and healthy controls are shown in table 2 and figure 2. ANOVA analysis of MBL2 levels between age groups 0-17, 18-35, 36-50, 51-65, and 65-80 showed no significant difference between the age groups ($p = 0.282$).

Table 2: MBL2 levels of study subjects according to age groups

Age Group	Malaria Cases	Healthy Controls
0-17	12.49 ± 11.76	21.40 ± 19.59
18-35	23.74 ± 20.91	14.00 ± 18.34
36-50	5.44 ± 2.31	12.80 ± 15.36
51-65	20.29 ± 13.73	18.90 ± 9.61
66-80	18.81 ± 15.4	37.01 ± 10.80

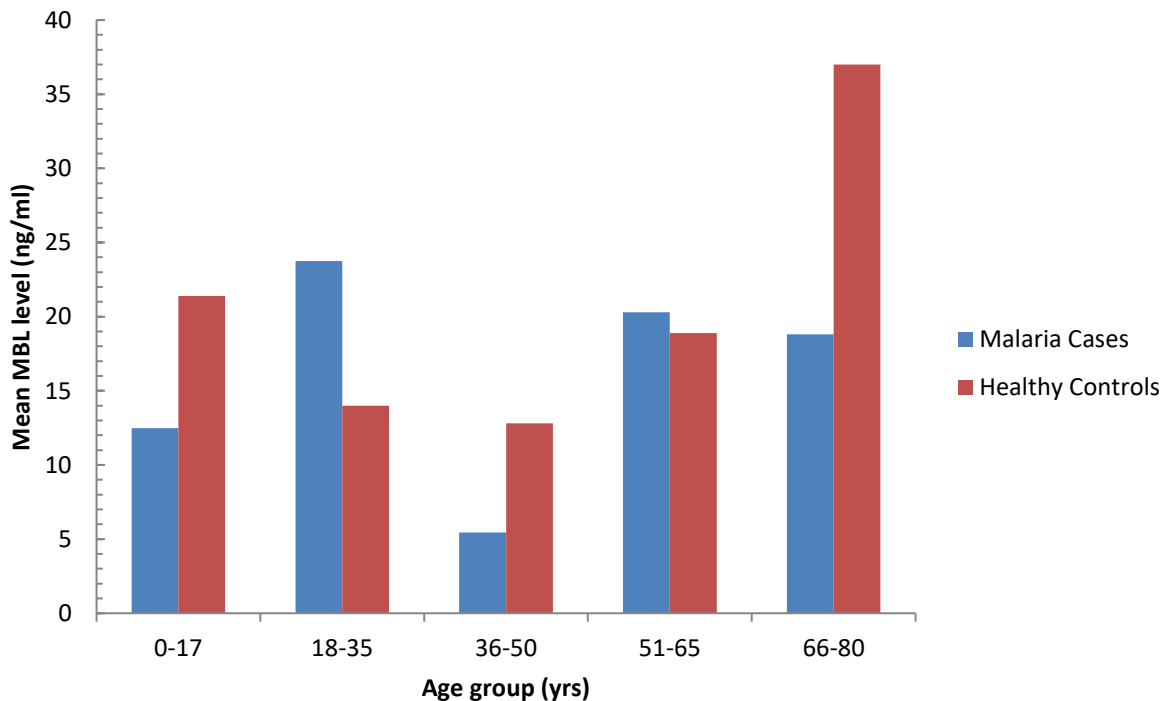


Fig. 2: Age-based mean MBL2 levels in malaria cases and healthy controls

4.0 Discussion

Mannose-binding lectin, a C-type, acute phase liver serum protein, is a major pathogen associated molecular pattern (PAMP) recognition molecule that plays an outstanding role in first line defense by binding to sugar moieties on the surface of microbes to activate

the lectin complement pathway and aid opsonophagocytosis (Neth *et al.*, 2002; Townsend *et al.*, 2001; Ying *et al.*, 2004).

The immune response of the protein is exhibited during acute phase response through an increase in its serum concentration (Ezekowitz *et al.*, 1991; Thiel *et al.*, 1992). The protein binds to

specific surface proteases on microbial surfaces to cause their destruction through the lectin complement pathway.

However, humans exhibit differential expression of MBL levels basically due to mutations in exon one and the promoter region of the MBL-2 gene (Eisen & Minchinton, 2003; Sumiya *et al.*, 1991). Individuals who have two copies of the wild type allele have been reported to have a mean serum level of approximately 1400µg/l while those who have a normal allele and the codon 54 mutant allele in conjunction with a particular promoter polymorphism exhibit mean MBL levels of between 26 and 396µg/l (Madsen *et al.*, 1995).

Boldt and Co-Workers (2006) suggested that malaria infection has a role to play in the evolution of MBL2 polymorphism among African populations due to their observed association between increased MBL protein levels and MBL2 variants among Gabonese children. The association of the MBL2 variants that result in low MBL plasma level and malaria susceptibility has also been established in other African and Indian populations (Holmberg *et al.*, 2008; Jha *et al.*, 2014; Luty *et al.*, 1998).

The above premises informed our investigation into a relationship between MBL levels and malaria symptoms among a Nigerian population resident in a *Plasmodium falciparum* halo-endemic region (Edet *et al.*, 2016). We obtained MBL serum levels of 14.41 ±13.04 ng/ml in malaria cases and 19.90 ±18.52ng/ml in healthy subjects. Grouping by age also shows differential serum MBL levels between cases and controls (table 2). Low MBL levels, occasioned by polymorphisms in the *MBL2* gene that brings about deficiency in innate immunity, have been suggested to be a contributing factor to childhood malaria morbidity (Boldt *et al.*, 2006; Eisen & Minchinton, 2003; Holmberg *et al.*, 2008; Luty *et al.*, 1998). However, there was no statistically significant difference in MBL

levels between our case and control groups; hence, there is no association between MBL levels and malaria in our study population. This result indicates that mannose binding lectin levels do not confer resistance to malaria among our study population.

5.0 Conclusion

The study showed that mannose binding lectin protein did not give protection against malaria in the population under study because variations in its level did not confer resistance against the disease.

Conflict Of Interest

The authors hereby declare that there is no conflict of interest in relation to this article.

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References

- Auriti, C., Prencipe, G., Moriondo, M., Bersani, I., Bertaina, C., Mondì, V., & Inglese, R. (2017). Mannose-Binding Lectin: Biologic Characteristics and Role in the Susceptibility to Infections and Ischemia-Reperfusion Related Injury in Critically Ill Neonates. *Journal of Immunology Research*, 2017. <https://doi.org/10.1155/2017/7045630>
- Bąk-Romaniszyn, L., Świerzko, A. S., Sokołowska, A., Durko, Ł., Mierzwa, G., Szala-Poździej, A., Małecka-Panas, E., & Cedzyński, M. (2020). Mannose-binding lectin (MBL) in adult patients with inflammatory bowel disease. *Immunobiology*, 225(1), 10–13. <https://doi.org/10.1016/j.imbio.2019.10.008>
- Bellamy, R., Ruwende, C., Mcadam, K. P. W. J., Thursz, M., Sumiya, M., Summerfield, J., Gilbert, S. C., Corrah, T., Kwiatkowski, D., Whittle, H. C., & Hill, A. V. S. (1998).

- Mannose binding protein deficiency is not associated with malaria, hepatitis B carriage nor tuberculosis in Africans. *QJM - Monthly Journal of the Association of Physicians*, 91(1), 13–18. <https://doi.org/10.1093/qjmed/91.1.13>
- Boldt, A. B., Messias-Reason, I. J., Lell, B., Issifou, S., Pedroso, M. L. A., Kremsner, P. G., & Kun, J. F. (2009). Haplotype specific-sequencing reveals MBL2 association with asymptomatic Plasmodium falciparum infection. *Malaria Journal*, 8(1), 1–7. <https://doi.org/10.1186/1475-2875-8-97>
- Boldt, A. B. W., Luty, A., Grobusch, M. P., Dietz, K., Dzeing, A., Kombila, M., Kremsner, P. G., & Kun, J. F. J. (2006). Association of a new mannose-binding lectin variant with severe malaria in Gabonese children. *Genes and Immunity*, 7(5), 393–400. <https://doi.org/10.1038/sj.gene.6364312>
- Cosar, H., Ozkinay, F., Onay, H., Bayram, N., Bakiler, A. R., Anil, M., Can, D., & Özkinay, C. (2008). Low levels of mannose-binding lectin confers protection against tuberculosis in Turkish children. *European Journal of Clinical Microbiology and Infectious Diseases*, 27(12), 1165–1169. <https://doi.org/10.1007/s10096-008-0573-8>
- Crompton, P. D., Pierce, S. K., & Miller, L. H. (2010). Advances and challenges in malaria vaccine development. *J Clin Invest*, 120(12), 4168–4178. <https://doi.org/10.1172/JCI44423>
- Denholm, J. T., McBryde, E. S., & Eisen, D. P. (2010). Mannose-binding lectin and susceptibility to tuberculosis: A meta-analysis. *Clinical and Experimental Immunology*, 162(1), 84–90. <https://doi.org/10.1111/j.1365-2249.2010.04221.x>
- Duffy, P. E., & Patrick Gorres, J. (2020). Malaria vaccines since 2000: progress, priorities, products. In *npj Vaccines* (Vol. 5, Issue 1, pp. 1–9). Springer US. <https://doi.org/10.1038/s41541-020-0196-3>
- Edet, U. O., Eban, R. U. B., Etok, C. A., & Ukanukumo, J. A. (2016). Prevalence of Malaria and Typhoid Co-infection amongst Residents of Uyo , Akwa Ibom State , Nigeria. *International Journal of TROPICAL DISEASE & Health*, 17(1), 1–6. <https://doi.org/10.9734/IJTDH/2016/25-920>
- Egbewande, O. M. (2022). The RTS,S malaria vaccine: Journey from conception to recommendation. *Public Health in Practice*, 4(June), 100283. <https://doi.org/10.1016/j.puhip.2022.100283>
- Eisen, D. P., & Minchinton, R. M. (2003). Impact of Mannose-Binding Lectin on Susceptibility to Infectious Diseases. *Clinical Infectious Diseases*, 37(11), 1496–1505. <https://doi.org/10.1086/-379324>
- Ezekowitz, R. A. B., Day, L. E., & Herman, G. A. (1991). A human mannose-binding protein is an acute-phase reactant that shares sequence homology with other vertebrate lectins. *Journal of Experimental Medicine*, 174(3), 1034–1046.
- Ezekowitz, R. A. B., Kuhlman, M., Groopman, J. E., & Byrn, R. A. (1989). A human serum mannose-binding protein inhibits in vitro infection by the human immuno-deficiency virus. *Journal of Experimental Medicine*, 169(1), 185–196. <https://doi.org/10.1084/jem.169.1.185>
- Ezekowitz, R. A., & Stahl, P. D. (1988). The structure and function of vertebrate mannose lectin-like proteins. *Journal of Cell Science. Supplement*, 9, 121–133. <https://doi.org/10.1242/jcs.1988.suppleme>

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- Florens, L., Washburn, M. P., Raine, J. D., Anthony, R. M., Grainger, M., Haynes, J. D., Moch, J. K., Muster, N., Sacci, J. B., Tabb, D. L., Witney, A. A., Wolters, D., Wu, Y., Gardner, M. J., Holder, A. A., Sinden, R. E., Yates, J. R., & Carucci, D. J. (2002). A proteomic view of the *Plasmodium falciparum* life cycle. *Nature*, *419*(6906), 520–526. <https://doi.org/10.1038/nature01107>
- Futagbi, G., Otu, P. S., Abdul-rahman, M., Aidoo, E. K., Lo, A. C., Gyan, B. A., Afrane, Y. A., & Amoah, L. E. (2022). *Malaria Outcomes in People in Southern Ghana. 2022.*
- Garcia-Laorden, M. I., Pena, M. J., Caminero, J. A., Garcia-Saavedra, A., Campos-Herrero, M. I., Caballero, A., & Rodriguez-Gallego, C. (2006). Influence of mannose-binding lectin on HIV infection and tuberculosis in a Western-European population. *Molecular Immunology*, *43*(14), 2143–2150. <https://doi.org/10.1016/j.molimm.2006.01.008>
- Gardner, M. J., Hall, N., Fung, E., White, O., Berriman, M., Hyman, R. W., Carlton, J. M., Pain, A., Nelson, K. E., Bowman, S., Paulsen, I. T., James, K., Eisen, J. A., Rutherford, K., Salzberg, S. L., Craig, A., Kyes, S., Chan, M. S., Nene, V., ... Barrell, B. (2002). Genome sequence of the human malaria parasite *Plasmodium falciparum*. *Nature*, *419*(6906), 498–511. <https://doi.org/10.1038/nature01097>
- Garred, P., Nielsen, M. A., Kurtzhals, J. A. L., Malhotra, R., Madsen, H. O., Goka, B. Q., Akanmori, B. D., Sim, R. B., & Hviid, L. (2003). Mannose-Binding Lectin Is a Disease Modifier in Clinical Malaria and May Function as Opsonin for *Plasmodium falciparum*-Infected Erythrocytes (*Infection and Immunity* (2003) 71:9 (5245-5253)). *Infection and Immunity*, *71*(11), 6687. <https://doi.org/10.1128/IAI.71.11.6687.2003>
- Holmberg, V., Schuster, F., Dietz, E., Sagarriga Visconti, J. C., Anemana, S. D., Bienzle, U., & Mockenhaupt, F. P. (2008). Mannose-binding lectin variant associated with severe malaria in young African children. *Microbes and Infection*, *10*(4), 342–348. <https://doi.org/10.1016/j.micinf.2007.12.008>
- Jack, D. L., & Turner, M. W. (2003). Antimicrobial activities of mannose-binding lectin. *Biochemical Society Transactions*, *31*(4), 753–757. <https://doi.org/10.1042/BST0310753>
- Jha, A. N., Sundaravadivel, P., Singh, V. K., Pati, S. S., Patra, P. K., Kremsner, P. G., Velavan, T. P., Singh, L., & Thangaraj, K. (2014). MBL2 variations and malaria susceptibility in Indian populations. *Infection and Immunity*, *82*(1), 52–61. <https://doi.org/10.1128/IAI.01041-13>
- Lambourne, J., Agranoff, D., Herbrecht, R., Buchbinder, A., Willis, F., Letscher-Bru, V., Agrawal, S., Doffman, S., Johnson, E., White, P. L., Barnes, R. A., Griffin, G., Lindsay, J. A., & Harrison, T. S. (2009). Association of mannose-binding lectin deficiency with acute invasive aspergillosis in immunocompromised patients. *Clinical Infectious Diseases*, *49*(10), 1486–1491. <https://doi.org/10.1086/644619>
- Larsen, F., Madsen, H. O., Sim, R. B., Koch, C., & Garred, P. (2004). Disease-associated mutations in human mannose-binding lectin compromise oligomerization and activity of the final protein. *Journal of Biological Chemistry*, *279*(20), 21302–21311. <https://doi.org/10.1074/jbc.M4005-20200>

- Lipscombe, R. J., Sumiya, M., Hill, A. V. S., Lau, Y. L., Levinsky, R. J., Summerfield, J. A., & Turner, M. W. (1993). High frequencies in African and non-African populations of independent mutation in the mannose binding protein gene. *Human Molecular Genetics*, 2(3), 342. <https://doi.org/10.1093/hmg/2.3.342>
- Luty, A. J. F., Kun, J. F. J., & Kremsner, P. G. (1998). Mannose-binding lectin plasma levels and gene polymorphisms in Plasmodium falciparum malaria. *Journal of Infectious Diseases*, 178(4), 1221–1224. <https://doi.org/10.1086/515690>
- Mascola, J. R., & Fauci, A. S. (2020). Novel vaccine technologies for the 21st century. *Nature Reviews Immunology*, 20(2), 87–88. <https://doi.org/10.1038/s41577-019-0243-3>
- Minchinton, R. M., Dean, M. M., Clark, T. R., Heatley, S., & Mullighan, C. G. (2002). Analysis of the relationship between mannose-binding lectin (MBL) genotype, MBL levels and function in an Australian blood donor population. *Scandinavian Journal of Immunology*, 56(6), 630–641. <https://doi.org/10.1046/j.1365-3083.2002.01167.x>
- Mombo, L. E., Lu, C. Y., Ossari, S., Bedjabaga, I., Sica, L., Krishnamoorthy, R., & Lapoumeroulie, C. (2003). Mannose-binding lectin alleles in sub-Saharan Africans and relation with susceptibility to infections. *Genes and Immunity*, 4(5), 362–367. <https://doi.org/10.1038/sj.gene.6363-979>
- Neth, O., Jack, D. L., Dodds, A. W., Holzel, H., Klein, N. J., & Turner, M. W. (2000). Mannose-binding lectin binds to a range of clinically relevant microorganisms and promotes complement deposition. *Infection and Immunity*, 68(2), 688–693. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L30056524%0Ahttp://dx.doi.org/10.1128/IAI.68.2.688-693.2000>
- Neth, O., Jack, D. L., Johnson, M., Klein, N. J., & Turner, M. W. (2002). Enhancement of Complement Activation and Opsonophagocytosis by Complexes of Mannose-Binding Lectin with Mannose-Binding Lectin-Associated Serine Protease After Binding to Staphylococcus aureus. *The Journal of Immunology*, 169(8), 4430–4436. <https://doi.org/10.4049/jimmunol.169.8.4430>
- Petersen, S. V., Thiel, S., & Jensenius, J. C. (2001). The mannan-binding lectin pathway of complement activation: Biology and disease association. *Molecular Immunology*, 38(2–3), 133–149. [https://doi.org/10.1016/S0161-5890\(01\)00038-4](https://doi.org/10.1016/S0161-5890(01)00038-4)
- Peterslund, N. A., Koch, C., Jensenius, J. C., & Thiel, S. (2001). Association between deficiency of mannose-binding lectin and severe infections after chemotherapy. *Lancet*, 358(9282), 637–638. [https://doi.org/10.1016/S0140-6736\(01\)05785-3](https://doi.org/10.1016/S0140-6736(01)05785-3)
- Rathnayake, D., Aitken, E. H., & Rogerson, S. J. (2021). Beyond Binding: The Outcomes of Antibody-Dependent Complement Activation in Human Malaria. *Frontiers in Immunology*, 12(June), 1 – 11. <https://doi.org/10.3389/fimmu.2021.683404>
- Sastry, K., Herman, G. A., Day, L., Deignan, E., Bruns, G., Morton, C. C., & Ezekowitz, R. A. B. (1989). The Human Mannose - Binding Protein Gene Exon Structure Reveals its Evolutionary Relationship to a Human Pulmonary Surfactant Gene and Localization to Chromosome 10. *J. Exp. MED*, 170 (October), 1175–1189.
- Shen, W., Xiao, L., Li, Y., Zhou, D., & Zhang,

- W. (2020). Association between polymorphisms in mannose-binding lectin 2 gene with pulmonary tuberculosis susceptibility. *Hereditas*, 157(1), 1–14. <https://doi.org/10.1186/s41065-020-00146-w>
- Sinka, M. E., Pironon, S., Massey, N. C., Longbottom, J., Hemingway, J., Moyes, C. L., & Willis, K. J. (2020). A new malaria vector in Africa: Predicting the expansion range of *Anopheles stephensi* and identifying the urban populations at risk. *Proceedings of the National Academy of Sciences of the United States of America*, 117(40), 24900–24908. <https://doi.org/10.1073/pnas.2003976117>
- Sumiya, M., Tabona, P., Arai, T., Summerfield, J. A., Super, M., Levinsky, R. J., & Turner, M. W. (1991). Molecular basis of opsonic defect in immunodeficient children. *The Lancet*, 337(8757), 1569–1570. [https://doi.org/10.1016/0140-6736\(91\)93263-9](https://doi.org/10.1016/0140-6736(91)93263-9)
- Takahashi, K., & Ezekowitz, R. A. B. (2005). The role of the mannose-binding lectin in innate immunity. *Clinical Infectious Diseases*, 41(SUPPL. 7), 335–339. <https://doi.org/10.1086/431987>
- Thiel, S., Holmskov, U., Hviid, L., Laursen, S. B., & Jensenius, J. C. (1992). The concentration of the C-type lectin, mannan-binding protein, in human plasma increases during an acute phase response. *Clinical and Experimental Immunology*, 90(1), 31–35. <https://doi.org/10.1111/j.1365-2249.1992.tb05827.x>
- Tong, X., Wan, Q., Li, Z., Liu, S., Huang, J., Wu, M., & Fan, H. (2019). Association between the mannose-binding lectin (MBL)-2 gene variants and serum MBL with pulmonary tuberculosis: An update meta-analysis and systematic review. *Microbial Pathogenesis*, 132(April), 374–380. <https://doi.org/10.1016/j.micpath.2019.04.023>
- Townsend, R., Read, R. C., Turner, M. W., Klein, N. J., & Jack, D. L. (2001). Differential recognition of obligate anaerobic bacteria by human mannose-binding lectin. *Clinical and Experimental Immunology*, 124(2), 223–228. <https://doi.org/10.1046/j.1365-2249.2001.01549.x>
- Turner, M. (1996). Mannose-binding lectin: the pluripotent molecule of the innate immune system. *Immunology Today*, 17(11), 532–539. [https://doi.org/10.1016/0167-5699\(96\)10062-1](https://doi.org/10.1016/0167-5699(96)10062-1)
- Udosen, I. U. & Nya, E. J. (2017). Association of MBL2 codon 34 variant of Exon 1 with severity of tuberculosis in Paediatric Population of South Africa. *Advances in Life Science and Technology* Volume 58: 1-9
- Udosen, I. U. (2019). Non-Association of Toll-Like Receptor 2 rs3804099 Polymorphism with Paediatric Tuberculosis in South Africa. *Advances in Life Science and Technology*, Volume 74:46-50.
- Udosen, I. U. (2020). Lack of association of toll-like receptor 2 rs3804100 Polymorphism with paediatric Tuberculosis in South Africa. *African Journal of Biotechnology*, Vol. 19:51-55.
- Udosen, I. U., Akpanabiatu, M. I., Samuel, A. E. & Sandy, I. Y. (2021) Mannose Binding Lectin levels was not Associated with Resistance to Tuberculosis Infection in the Population of Uyo Metropolis in Nigeria. *Journal of Natural Sciences Research*, Volume 12(14): 13-17.
- World Health Organisation. (2022). WHO launches new initiative to stop the spread of invasive malaria vector in Africa. <https://www.who.int/news/item/29-09-2022>

2022-who-launches-new-initiative-to-stop-the-spread-of-invasive-malaria-vector-in-africa#:~:text=In a 2019 vector alert,mosquito species in the region.

World Health Organization. (2019). Vector alert: Anopheles stephensi invasion and spread. In <https://www.who.int/publications/i/item/WHO-HTM-GMP-2019.09>.

<https://apps.who.int/iris/bitstream/handle/10665/326595/WHO-HTM-GMP-2019.09-eng.pdf?sequence=1&isAllowed=y>

World Health Organization. (2022a). *WHO initiative to stop the spread of Anopheles stephensi in Africa*. <https://www.who.int/publications/i/item/WHO-UCN-GMP-2022.06>

World Health Organization. (2022b). *World malaria report 2022*. World Health Organization, Geneva.

Ying, H., Ji, X., Hart, M. L., Gupta, K., Saifuddin, M., Zariffard, M. R., & Spear, G. T. (2004). Interaction of mannose-binding lectin with HIV type 1 is sufficient for virus opsonization but not neutralization. *AIDS Research and Human Retroviruses*, 20(3), 327–335. <https://doi.org/10.1089/088922204322996563>

Zavala, F. (2022). RTS,S: the first malaria vaccine. *Journal of Clinical Investigation*, 132(1). <https://doi.org/10.1172/JCI156588>