

## DOES VITAMIN D REDUCE THE MORTALITY RATE OF PLASMODIUM INFECTION? : A SYSTEMATIC REVIEW

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### Abstract

**Background:** Malaria is widespread in tropical and subtropical regions, causing more than 300 million acute illnesses and resulting in more than 600,000 deaths annually. Vitamin D (VD) is a fat-soluble vitamin that is synthesized in the skin after exposure to solar ultraviolet B radiation or provided in food. In addition to its traditionally recognized role in the regulation of bone metabolism and calcium-phosphorus homeostasis, VD is increasingly recognized to have prominent regulatory functions in both the innate and adaptive immune systems.

**The aim:** This study aims to show that vitamin D reduce the mortality rate of plasmodium infection or not.

**Methods:** By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

**Result:** In the PubMed database, the results of our search brought up 411 articles, whereas the results of our search on SagePub brought up 49 articles. The results of the search conducted for the last year of 2013 yielded a total 362 articles for PubMed and 36 articles for SagePub. The result from title screening, a total 4 articles for PubMed and 16 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria. **Conclusion:** Vitamin D affects the survival rate of individuals infected with Plasmodium. Although mouse models may not accurately reproduce the clinical picture and pathophysiology of malaria in humans, the studies conducted have been instrumental in providing information on how to design appropriate studies in humans.

**Keyword:** Vitamin D, Plasmodium Infection, Malaria

## INTRODUCTION

Malaria is a disease caused by Plasmodium infection in humans. The incidence of malaria is estimated to exceed 216 million clinical cases per year, with 445,000 deaths reported annually. Despite intensive intervention efforts, estimated morbidity and mortality rates continue to increase. Chemotherapy and vector control programs have been largely ineffective, due to the emergence and spread of insecticide-resistant mosquito vectors and drug-resistant plasmodium strains.<sup>1</sup>

According to the World Health Organization (WHO), the incidence of malaria cases has been decreasing globally since 2010, but the rate of decline has stopped since 2014. Malaria is still a public health burden, especially in Sub-Saharan Africa, where it accounts for around 90% of the total Malaria cases and deaths worldwide. The number of deaths from malaria in the WHO region of Africa is estimated at 407,000 in 2016.<sup>2</sup>

Vitamin D is a secosteroid hormone that regulates the expression of nearly 900 genes and is involved in the regulation of calcium and phosphate metabolism, immune responses, and brain development. Low blood levels of vitamin D have been reported in patients affected by infectious diseases, including those caused by parasites. Among these is the pathogen that causes malaria in humans, Plasmodium falciparum, which was responsible for the deaths of nearly 365,000 children under the age of five in Africa in 2016. Although currently available antimalarial drugs are very effective, malaria has high morbidity and mortality, thus causing death. This means the search for additional therapies to be administered alongside antimalarial treatment is growing rapidly.<sup>3</sup>

Vitamin D3 (VD3, calcitriol), the active form of vitamin D, exhibits antimalarial activity. There, we emphasized that VD3 extensively inhibited parasite growth during the acute phase and subsequent parasite growth, forming a mild delayed peak that terminated naturally. In this study, we aimed to clarify the mechanisms underlying the extensive inhibition of parasitemia in the acute phase. Initially, we hypothesized that the antimalarial properties of VD3 were due to changes in nitric oxide (NO) levels, because VD3 is a known NO inducer, and NO is known to inhibit the growth of several microorganisms. That is, we envision a scenario in which VD3 exhibits antimalarial activity through NO production.<sup>1</sup>

Improvements in malaria control interventions have resulted in reductions in morbidity and mortality due to malaria. Since 2014 progress has slowed and the number of malaria cases has even increased in some countries. Reports from Sub-Saharan Africa show that Plasmodium falciparum infections are more common in school-aged children than in young children and adults. 200 million school-aged children are at risk of malaria in Africa, in many regions where the prevalence of infection exceeds 50% in this age group. This infection is associated with health problems, anemia, decreased cognitive function, and low educational achievement. Infections in school-age children are also an important source of human-to-mosquito transmission of P falciparum, which promotes malaria transmission and hinders malaria elimination efforts. Innovative interventions are urgently needed to protect these children from the impact of P falciparum infections and to reduce the reservoir of P falciparum circulating in endemic communities.<sup>4</sup>

## METHODS

### Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

### Criteria for Eligibility

For the purpose of this literature review, we compare and contrast of vitamin D reduce the mortality rate of plasmodium infection or not. It is possible to accomplish this by researching or investigating the effectiveness of vitamin D to reduce the mortality rate of plasmodium infection. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine the best time to perform emergency surgery for congenital diaphragmatic hernia. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

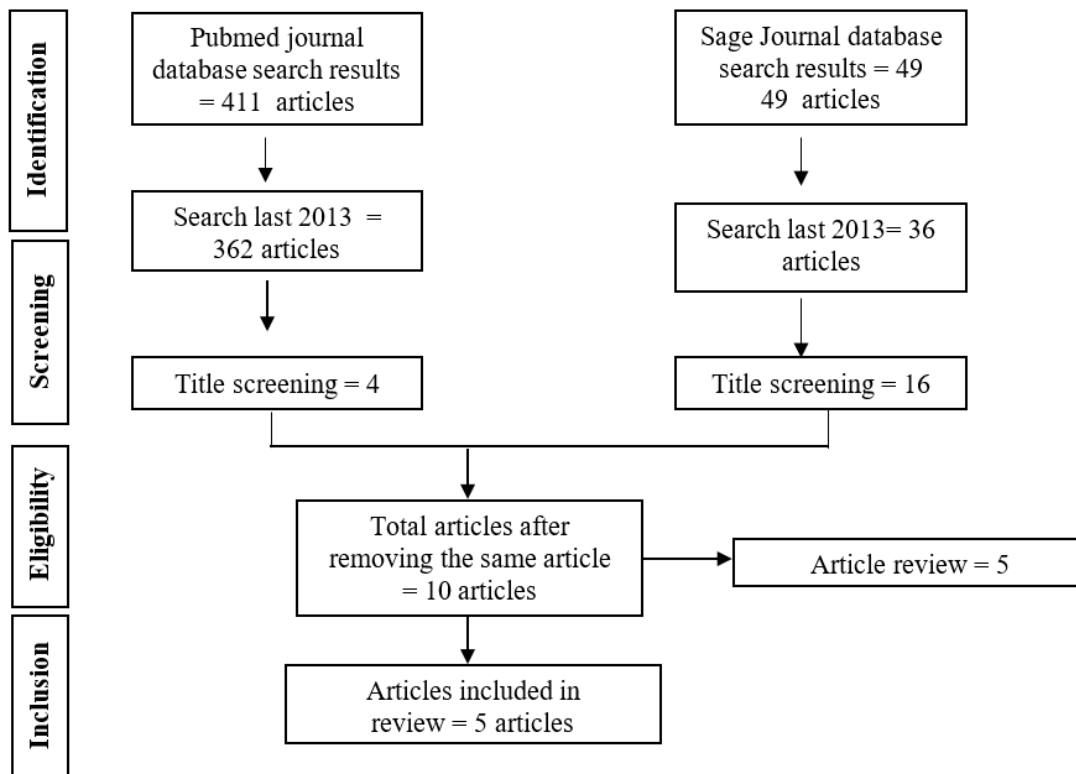
### Search Strategy

We used "Vitamin D Reduce the Mortality Rate of Plasmodium Infection"; "the efficacy of vitamin D for plasmodium infection" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: (*"Vitamin D for Plasmodium Infection"*[MeSH Subheading] OR *"Efficacy vitamin D to reduce the mortality rate of plasmodium infection"*[All Fields] OR *"Vitamin D"*[All Fields]) AND (*"Plasmodium Infection"*[All Fields] OR *"efficacy of vitamin D for infection"*[All Fields]) AND (*"ercalcidiol"*[MeSH Terms] OR (*"cholecalciferol"*[All Fields]) OR (*"25-hydroxycholecalciferol"*[All Fields]) AND *"mortality rate of plasmodium*

*infection"[All Fields]) OR ("prevalence of plasmodium infection"[All Fields]) OR ("plasmodium"[All Fields]) OR ("incident of plasmodium infection"[All Fields]) AND "the impact of vitamin D")]) used in searching the literature.*

**Data retrieval**

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.



**Figure 1. Article search flowchart**

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

**Quality Assessment and Data Synthesis**

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. In order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

**RESULT**

In the PubMed database, the results of our search brought up 411 articles, whereas the results of our search on SagePub brought up 49 articles. The results of the search conducted for the last year of 2013 yielded a total 362 articles for PubMed and 36 articles for SagePub. The result from title screening, a total 4 articles for PubMed and 16 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.

Setto et al (2022)<sup>5</sup> showed serum 25(OH)D concentrations were within normal levels (>20 ng/mL) in the malaria group and control group, with a mean value of 32.3±11.9 ng/mL respectively and 34.7±11.5 ng/mL, and there was no significant difference between groups (p=0.11, t-test). Low serum 25(OH)D levels were seen in 28.5% (35 of 123) of malaria patients and 24.6% (30 of 122) of the control group, without significant difference (p=0.58, Pearson's chi . square test). Malaria patients in mining areas had a mean 25(OH)D value (32.2 ng/mL) which was much lower than controls in mining areas (38.3 ng/mL; p=0.01; t-test), but both values are within the reference range. In terms of the plasmodial species involved (p=0.42, Fisher's exact test), there was no statistical difference between the frequency of low serum 25(OH)D levels in

individuals infected with *P. vivax* malaria (29.2% (33 of 113)) compared with individuals infected with *P. falciparum* malaria (20% (2 of 10)).

Workineh *et al* (2021)<sup>6</sup> showed The geometric mean parasite density was 38 572.58 parasites/μl blood, with minimum and maximum parasite densities of 4800 and 68000 parasites/μl blood, respectively. Moderate parasitemia was most common, followed by low parasitemia, which accounted for 44 (71%) and 10 (16.1%) of parasite densities, respectively. High parasitemia was found the least, namely 8% of the total (12.9%). Men were found to have a greater prevalence of moderate malaria parasitemia than women, namely 73.7% of the total. However, there was no statistical difference in parasite density between males and females ( $P = 0.956$ ). Although moderate parasitemia had the highest parasite density in the 6 to 10 year age group, there was no statistical significance between age groups in terms of parasitemia ( $P = 0.291$ ). Although there was no statistical difference ( $P = 0.956$ ), 72.4% of rural residents experienced moderate parasitemia compared to urban residents.

**Table 1. The litelature include in this study**

Author	Origin	Method	Sample Size	Result
Setto <i>et al.</i> , 2022 <sup>5</sup>	America	Cross-sectinal Study	123 patients with malaria and 122 individuals without malaria	Malaria patients residing in a mining area had 25(OH)D serum levels that were significantly lower than those in the control group residing in the mining area, though both were within normal levels. Red blood cell counts had an inverse correlation with parasitemia ( <i>Plasmodium falciparum</i> ), and platelet levels had an inverse correlation with parasitemia ( <i>Plasmodium vivax</i> ). 25(OH)D deficiency was evidenced in Itaituba, in the state of Pará, which is an endemic area of malaria in the Amazon region.
Workineh <i>et al.</i> , 2021 <sup>6</sup>	Africa	A prospective cross-sectional study	422 children	Malaria was found in 14.7% (95% CI 11.4-18.0) of the study participants. <i>P. falciparum</i> and <i>P. vivax</i> were found in 38 (61.3%) and 21 (33.9%) of the infected children, respectively. Mixed infections were found in 3 (4.8%) of the children.
He <i>et al.</i> , 2014 <sup>7</sup>	China	Experimental study	Mice	Preliminary experiments using a dose response of oral VD showed that there was no effect of 10 μg/kg, and 250 μg/kg VD as compared to the controls. In contrast, the mice treated orally with 50 μg/kg VD did not develop ECM. Therefore, we selected the 50 μg/kg dosage for subsequent experiments. VD supplementation prior to and 2 days after infection was effective at raising the serum 25(OH)D3 levels of mice. On day 5 p.i., the 25(OH)D3 levels in the VD-treated groups were significantly higher than that in the untreated PbA group. The four doses of VD in the VD-treated groups were enough to significantly raise serum 25(OH)D3 levels. There was no effect of the infection on serum 25(OH)D3 levels since vitamin D status was the same in the healthy control mice and the PbA-infected mice.
Yamamoto <i>et al.</i> , 2019 <sup>1</sup>	Japan	Experimental study	Mice	NO levels were higher in VD3-treated mice than in vehicle controls during the acute phase of PcAS infection; therefore, we hypothesized that NO levels during the early stage of infection would correspond to the antimalarial activity of VD3. NO levels in VD3-treated samples from day 2 and day 3 post-infection were significantly different from those in the vehicle control samples ( $P = 0.023$ and $0.032$ , respectively). It was confirmed that NO was greater in day 2 samples than in day 3 samples; moreover, 5 of 6 vehicle control mice died (83% mortality), while 83% of VD3-administered mice survived following extensive inhibition of acute phase parasitemia. To determine the effects of VD3 alone in vivo, we administered VD3 to non-infected mice. NO levels were the same between PcAS-infected and uninfected mice treated with VD3 on days 2 and 3. These results suggest that high NO levels induce antimalarial effects.
Dwivedi <i>et al.</i> , 2016 <sup>8</sup>	India	Experimental study	Mice	A significant difference in survival was observed in the entire treatment groups vs infected control group. In the PbA + VD and PbA + ART groups, more than half of the mice died even before completion of treatment. The majority of the deaths in all the treated groups were within 24 h after appearance of the symptoms suggesting that 12–24 h window is a critical time point to attain clinical recovery if the treatment is effective. In the PbA + ART–VD group, the significant survival of 73% was observed as compared to other treated groups ( $P^{***} = 0.004$ PbA + ART–VD vs PbA + ART, $P^{***} < 0.0001$ (PbA + ART–VD vs PbA + VD), $P^{***} < 0.0001$ (PbA + ART–VD vs PbA).

He *et al* (2021)<sup>7</sup> showed three VD treatment schemes offered mice significant protection against ECM. In the control group, PbA infection resulted in the onset of neurological symptoms on days 5–6 and mice began to die on days 6–7, with all mice dying on day 11 p.i. Death after PbA infection occurs in mice that have relatively low parasitemia (<12%). In PbA-infected mice, the vehicle (soybean oil) control group had symptoms (pathology, survival, or parasitemia) identical to the untreated group (data not shown). VD treatment before or 2 days after PbA infection protected mice from premature death and all VD-treated mice survived after day 16 postinfection. VD administration began on day 5 p.i. also offered mice protection from premature mortality with no deaths in this group before day 11. Regardless of VD treatment, all PbA-infected mice died from anemia with high parasitemia after ~3 weeks. There was a benefit to VD supplementation on day 2 p.i. because the PbA+VD2d group survived significantly longer (Kaplan-Meier test,  $P < 0.05$ ) than the other two VD treatment groups. In addition, parasitemia in the PbA+VD2d and PbA+VD5d groups was lower than in the VD+PbA group.

Yamamoto *et al* (2019)<sup>1</sup> showed no production in PcAS-infected mice treated with VD3 was measured before any experiments. Serum samples from two different bleeding protocols were prepared. The first set of samples was obtained on non-even days (i.e., 1, 3, 5 and 7) after VD3 administration; second set, on even days (2, 4, 6 and 8). Serum NO levels in control mice or mice treated with VD3 increased with increasing number of days post-infection until day 5-6 post-infection, showing an increasing trend in mice treated with VD3 compared with control mice. We noticed that on day 2 or day 3, samples treated with VD3 showed greater activity than the group treated with vehicle. The high NO production in VD3-treated mice in the acute phase was also verified in another experiment, in which blood samples were obtained sequentially from days 1–5. Surprisingly, the NO values in VD3-treated mice increased suddenly, showing a significant difference at day 2 postinfection, and the titers reached a 2-fold difference compared with the control group. This increase in NO levels was also observed in the day 3 samples, although the difference was not significant due to mass scattering. Thereafter, on days 4–5, the titers in VD3-treated mice and control mice became more similar due to the increase in titers in the control group. Considering these results, subsequent analyzes focused on NO production at days 2 and 3 postinfection, as the early behavior of NO at these stages is thought to be important to explain the extensive suppression of acute-phase parasitemia by VD3.

Dwivedi *et al* (2016)<sup>8</sup> showed A significant difference in survival was observed in the entire treatment groups vs infected control group. In the PbA + VD and PbA + ART groups, more than half of the mice died even before completion of treatment. The majority of the deaths in all the treated groups were within 24 h after appearance of the symptoms suggesting that 12–24 h window is a critical time point to attain clinical recovery if the treatment is effective. In the PbA + ART–VD group, the significant survival of 73% was observed as compared to other treated groups ( $P^{**} = 0.004$  PbA + ART–VD vs PbA + ART,  $P^{***} < 0.0001$  (PbA + ART–VD vs PbA + VD),  $P^{***} < 0.0001$  (PbA + ART–VD vs PbA). In the PbA + ART group, 43% mice recovered from ECM and remained negative throughout, but one mouse died on day 15 without any parasitaemia, thus reducing the survival from 43 to 29%. The mice that died in between was due to anaemia but no parasitaemia suggesting that even the effective antimalarial like arteether can control parasitaemia but the neurological deficit post-treatment leads to death of a certain per cent of survivors. A sharp decline in parasitaemia from  $18.34 \pm 2.94$  and  $17.20 \pm 1.50$  on day 6 to  $0.30 \pm 0.10$  and  $1.90 \pm 0.70$  on day 8 was evident in the surviving mice of PbA + ART and PbA + ART–VD group respectively.

## DISCUSSION

Malaria is a parasitic disease that attacks tropical and subtropical regions of the world. This disease is a significant cause of death, especially among pregnant women and children under five in endemic areas such as Sub-Saharan Africa. The World Health Organization (WHO) reports that almost half of the world's population is at risk of contracting malaria. Six species of Plasmodium are known to infect humans, all of which cause anemia. However, severe malaria is caused by infection with Plasmodium falciparum and Plasmodium vivax, with the former species causing the most severe forms of the disease, including cerebral malaria (CM) and severe anemia, which are the main causes of death in children under five.<sup>9,10</sup>

Malaria has a huge impact on society. Of the 228 million malaria cases reported globally in 2018 by the World Health Organization (WHO), an estimated 93% occurred in Africa. To achieve the goal of eradicating malaria, the global malaria community must mobilize its resources strategically to achieve major impact. This resource mobilization includes partners who are ready to address program challenges at the community level.<sup>11</sup>

The Plasmodium species that causes severe cases of malaria is Plasmodium falciparum. Clinical and laboratory features of severe malaria are cerebral malaria, generalized seizures, severe anemia (hemoglobin concentration  $< 7$  g/dL in adults,  $\leq 5$ g/dL in children  $< 12$  years), hypoglycemia (blood glucose  $< 40$  mg/dL), acidosis metabolic (plasma bicarbonate level  $< 15$  mmol/L or venous plasma lactate  $\geq 5$  mmol/L), hyperparasitemia (Plasmodium falciparum parasitemia  $> 10\%$ ), acute renal failure, acute pulmonary edema, impaired consciousness, circulatory shock, abnormal bleeding, coagulation disseminated intravascular disease, jaundice, hemoglobinuria, and high fever. Immediate treatment with an effective antimalarial regimen is recommended to prevent disease progression to severe malaria.<sup>12,13</sup>

Vitamin D (VD) is a fat-soluble vitamin that is synthesized in the skin after exposure to solar ultraviolet B radiation or provided in food. In addition to its traditionally recognized role in the regulation of bone metabolism and calcium-



phosphorus homeostasis, VD is increasingly recognized to have prominent regulatory functions in the innate and adaptive immune systems. The active form of VD [1,25(OH)2D3, 1,25D3] mainly affects the maturation of dendritic cells (DC) and macrophage differentiation, and inhibits the production of cytokines IL-12 and IL-23. In addition, 1,25D3 inhibits the production of Th1 cytokines (IL-2 and IFN- $\gamma$ ) and Th17 cytokines (IL-17 and IL-21), but stimulates the production of Th2 cytokines (e.g. IL-4), thereby indirectly shifting polarization. T cells from Th1 and Th17 phenotypes to Th2 phenotypes. Additionally, 1,25D3 supports Treg development through DC modulation. Since many autoimmune diseases such as inflammatory bowel disease, multiple sclerosis, and arthritis are the result of excessive Th1 responses, 1,25D3 treatment suppresses Th1 responses and ameliorate Th1-mediated experimental autoimmunity. Paradoxically, although VD inhibits Th1 and Th17 responses, a number of infectious diseases are not made worse by treatment with active VD.<sup>7</sup> Malaria patients living in mining areas had lower 25(OH)D levels than the control group living in mining areas. Serum platelet levels had a significant inverse correlation with parasitemia (*P. vivax*) and time to disease progression. Serum red blood cell levels had a significant inverse correlation with parasitemia (*P. falciparum*). Compared with patients with a previous history of malaria, patients with a first infection experienced a significant decrease in serum leukocyte levels.<sup>5,14</sup>

## CONCLUSION

Vitamin D affects the survival rate of individuals infected with Plasmodium. Although mouse models may not accurately reproduce the clinical picture and pathophysiology of malaria in humans, the studies conducted have been instrumental in providing information on how to design appropriate studies in humans. However, this study is a systematic review and meta-analysis that addresses the effects of vitamin D on Plasmodium infections. Further research should be conducted to investigate the impact of vitamin D on malaria in the future.

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