**VDR LOWERS THE RISK OF INFECTION TO IMPROVE THE QUALITY OF NURSING SERVICES: A SYSTEMATIC REVIEW**

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***Abstract***

***Background:*** The high prevalence of infection reaches 7.1% in European countries, 4.5% in the US, and ranges from 3.5% to 12% in other developed countries. The discovery of VDR has become one of the solutions in reducing the risk of infection, where VDR acts as a transcription factor by modulating gene expression that triggers the immune response to the infection.

***Objectives:*** This study aims to systematically evaluate and describe the role of VDR in reducing the risk of infection to improve the quality of nursing services.

***Methods:*** A systematic literature search was conducted on 5 databases, namely Google Scholar, PubMed, ProQuest, Sage, and ScienceDirect for articles published in the last 5 years in English, related to the role of VDR in reducing infections in nursing.

***Results:*** Based on the analysis of 10 articles, VDR plays a role in inhibiting cancer cell proliferation, killing bacteria in typhoid fever, playing a protective role against bacterial challenges, regulating intestinal homeostasis by preventing the invasion of pathogenic bacteria, acting as a potent immunomodulator and antimicrobial agent, mediating protection against infections by supporting antiviral responses, acting as an anti-inflammatory, antiproliferative, and antitumorigenic agent, and alleviating intestinal fibrosis by inhibiting EMT (Epithelial-Mesenchymal Transition).

***Conclusion:*** VDR reduces the risk of infection by killing bacteria and viruses, especially in the intestine, controlling gastrointestinal homeostasis, acting as an anti-inflammatory and antiproliferative agent, and playing a prognostic role.

***Keywords :****VDR, Infection, Nursing*

1. **Introduction**

Infectious diseases are still a health problem that causes morbidity and mortality that attract attention in both developing and developed countries [1]. In addition to causing large numbers of deaths and creating socioeconomic vulnerabilities, high infections will also cause a surge in health worker mobilization [2].

 Currently, the prevalence of infectious diseases reported by the *European Centre for Disease Prevention and Control* (ECDC) in 2022 is 7.1% in European countries, 4.5% in the United States (US) and ranges from 3.5% to 12% in other developed countries [3]. The high rate of infection affects health workers, especially nurses as 24-hour standby personnel who are at the patient's side to provide nursing care [4]. Nurses will experience extreme pressures, suffer from psychological disorders and have a higher risk of infection and will even experience stigmatization from society [5].

Several efforts have been made to reduce infection rates such as training to all health workers according to their needs [6]. In addition, nurses also make independent efforts using adequate personal protective equipment to protect patients from various microorganisms and themselves during their duties [7]. However, this is not enough to reduce the risk of infection. It requires a component that supports immune function in warding off viruses and bacteria that cause infection.

In recent years, vitamin D has become a hot topic in the world of health and a material for research, especially with the discovery of VDR. It is known that VDR can lower the risk of infection [8] by regulating several genes such as cathelicidin which plays a role in the activation of macrophages, neutrophils, dendritic cells, and beta defensin which can directly break down the viral membrane [9].

The VDR acts as a transcription factor that modulates the expression of genes that trigger an immune response to viral infections [10]. In addition, VD/VDR can increase innate immunity and antimicrobial expression which is key to the antiviral process. VDR is also able to increase the production of anti-inflammatory cytokines and avoid excessive inflammatory responses [11].

Currently, there is a lot of literature that reveals the role and benefits of VDR. However, there has been no article that summarizes the important role of VDR in lowering the risk of infection for improved nursing services. *The International Council of Nurses* (2021) states that one indicator of improving the quality of nursing services is a decrease in morbidity and death rates caused by infection [12]. Based on this, the author intends to summarize the important role of VDR in reducing infection rates to improve nursing services.

1. **Methods**

Systematic review, which is the method used in this article, is a scientifically rigorous methodological study in compiling empirical evidence and producing more accurate and reliable conclusions [13]. Systematic review search protocols are designed critically from scientific studies to obtain relevant results through searching, identifying, assessing and evaluating evidence-based studies [14].

The preparation for systematic review using Prisma Checklist 2020 guidelines contains a 27-item checklist and a four-phase flowchart that characterizes academics in publications to help making critical and comprehensive evaluation [15]. To assess the notability of the article, the author uses *Critical Appraisal Skill Programme* (CASP) (Critical Appraisal Skills Programme, 2018) and *Centre for Evidence-Based Medicine* (CEBM) tool *(Center for Evidence-Based Medicine*, 2014)*.*

The literature search was carried out in 5 databases, i.e., *Google Scholar* (n=3,260), *PubMed* (n=172), *ProQuest* (n=162), *Sage* (n=84), dan *ScienceDirect* (n= 65). A total of 3,743 articles were identified from all five database searches that have been filtered into the last 5 years. However, after the screening, only 36 articles were found matching the title of this study.

Furthermore, screening was carried out to assess the eligibility of articles based on inclusion and exclusion criteria. Of the 36 articles, 26 were excluded because they did not meet the inclusion criteria, for the reason of double publication (n = 5), qualitative research design (n = 4), not research results (n = 8), and abstract (n = 9). Thus, only 11 articles met the inclusion criteria.

Articles included for this literature review are those that (1) focus on VDR and infection; (2) is written in English; (3) was published in the last 5 years, namely from 2018-2022; and (4) are articles on nursing.



Figure 1: Flowchart of the Article Selection

# Results

### *Method*

Of the 11 articles selected, there are 5 methods used, namely *Cross-sectional* (n=3), *Systematic review* (n=2), *Meta-analysis* (n=2), *Cohort Study* (n=3), and *Experimental in vivo* (n=1). Research from the 11 articles was conducted in several countries, namely China (n=3), Indonesia (n=2), Sweden (n=1), AS (n=1), UK (n=1), Egypt (n=1), and Russia (n=1).

***Sample***

 From 11 articles included, Huss et al.'s (2019) research used a sample of 718 women with invasive breast tumor [16]. A similar research by M. Yu et al., 2021 used 19 intestinal tissue samples [17]. In the research by H. O. U. Yu et al., (2022) the samples were 10 articles from 5 databases regarding ARDS disease [11]. In Sun & Zhang's research, (2022) searches on PubMed and Google Scholar focused on VDR and intestine [18].

 Other studies were carried out by Zhao et al., (2018) with a sample of 14 people with buccal mucosal sites [19] and Jolliffe et al., (2018) with a sample of 725 participants with respiratory infection [20]. In Febriza et al.'s research, (2020) sample was 30 mice [21]. In the research of Wardani et al., (2021), the sample was 39 people with HIV infection [22]. Another research was by Abdel-Mohsen et al., (2018) with sampling 90 people with healthy subjects and Hepatitis C [23]. In the research by Guzeeva et al., (2019) the sample was 51 adolescents with helicobacter pylori infection (HP) [24]. O'Brien's (2018) research involved a sample of 1070 cases with non-Hispanic white female respondents.

 ***Results***

 Several studies have been conducted to evaluate the important role of VDR in lowering the risk of infection in order to improve the quality of nursing services. There are 11 articles that meet the inclusion and exclusion criteria. In a research by Huss et al., (2019), VDR acts as a prognostic factor in reducing the risk of death from breast cancer by inhibiting the proliferation of cancer cells. Another research by Febriza et al., (2020) proved that VDR kills bacteria in typhoid fever.

 A similar research by Zhao et al.,( (2018) suggests that VDR plays a protective role to overcome bacterial challenges, stopping or delaying the progression of Oral Lichen Planus (OLP). Furthermore, Sun & Zhang's (2020) research suggests that VDR plays a role in regulating intestinal homeostasis by preventing the invasion of pathogenic bacteria, inhibiting inflammation, and maintaining barrier function. Furthermore, in the research by Wardani et al., (2021) VDR became a strong immunomodulator and antimicrobial effect against HIV infection.

 Research by Jolliffe et al., (2018) suggests that VDR plays a role in mediating protection against upper respiratory tract infections by supporting antiviral responses. The result of Abdel-Mohsen et al.'s (2018) research showed that VDR acts as an anti-inflammatory, antiproliferative, and antitumorgenesis in Hepatitis C. Research by M. Yu et al., (2021) found that VDR can relieve intestinal fibrosis in Crohn's disease by inhibiting Epithelial-mesenchymal transition (EMT) through regulation of epithelial mitochondrial function. Another research by Guzeeva et al., (2019) proved that VDR helps kill bacteria and reduce infection due to Helicobacter Pylori in chronic gastroduodenitis. O'Brien's research, (2018) also proved that CpGs methylation in vitamin D-related genes might interact with 25(OH)D to lower breast cancer risk.

1. **Discussion**

***Method***

Based on the reviewed articles, cross-sectional is the most widely used method, where the design of this study was carried out to determine the role of VDR in several diseases by observing several sample groups at the same time.

Cross-sectional study design is an observational design that involves and looks at data from the population at one particular point in time to measure the results and exposure of research subjects and at the same time be the most relevant research in understanding the prevalence of a disease [25]. Thus, it is the most suitable design used to evaluate the role of VDR in several diseases

***Sample***

From the literature review conducted, it was found that the largest number of samples that are often used on average is <30 - <90 subjects. This is consistent with the statement that cross-sectional using a sample selected from the available population has potential relevance to the research question and the sample can be categorized in several groups [26][25].

Meanwhile, the characteristics of respondents were dominated by infectious patients including HIV, respiratory tract infections, tuberculosis, and hepatitis C. VDR has a special role against infection and direct antiviral effects [27].

***The Role of VDR in Reducing Infection***

 Several reviewed articles point to the important role of VDR in lowering the risk of infection. One well-known target network of VDR is the intestinal tract. VDR specifically activates cells in the intestinal epithelium (e.g. Paneth cells) and lamina propria (e.g. B cells/plasma cells) to restrict the entry of microbiota (and/or their products) into the interstitium [28]. This theory is in line with 3 articles reviewed, including the research by Febriza et al., 2020 which emphasizes the role of VDR in killing bacteria in the intestine, especially in typhoid fever. The higher the VDR level, the lower the number of bacterial colonies is [21]. In Sun & Zhang's research, (2022) it is said that VDR is very important in regulating intestinal homeostasis by preventing the invasion of pathogenic bacteria, inhibiting inflammation, and maintaining barrier functions [18]. Similar findings by M. Yu et al., 2021 showed that VDR significantly alleviates intestinal fibrosis by inhibiting fibroblast activation, maintaining epithelial mitochondrial function, and reducing EMT processes [17].

 In addition to the intestine, VDR is also found in the stomach which plays a role in controlling gastrointestinal homeostasis by regulating epithelial cells, innate immune cells, and acquired immune cells [29]. This theory is in line with the research by Guzeeva et al., (2019) that VDR levels help kill and reduce infection due to Helicobacter Pylori in chronic gastroduodenitis [24].

 Another theory reveals that VDR can activate antimicrobial peptides secreted on mucosal surfaces and has the ability to kill bacteria and viruses [30]. It is in line with the reviewed article in the research by Wardani et al., (2021) that VDR has a strong immunomodulatory effect and antimicrobial effect on HIV infection [22]. In addition, Zhao et al., (2018) stated that VDR plays a protective role in the integrity of the oral mucosal barrier to overcome bacterial challenges, stopping or delaying the development of Oral Lichen Planus [19]. This is reinforced by the research by Jolliffe et al., (2018) that VDR mediates protection against respiratory infections by supporting antiviral responses [20].

 In addition, VDR plays an important role as an anti-inflammatory agent [31]. This is in line with the research by H. O. U. Yu et al., (2022), which found that VDR works as an anti-inflammatory in acute breathing by inhibiting TNF/NF-κB and IFN-γ signalling pathways and reducing the production of pro-inflammatory cytokines such as IL-6 [11]. Meanwhile, in the research by Abdel-Mohsen et al., (2018), it was found that VDR also plays a role as an anti-inflammatory, antiproliferative, and antitumor genesis so as to inhibit inflammation in Hepatitis C [23].

 Another theory is that VDR works as an anti-proliferation in cancer. This is in line with the article reviewed in the research by Huss et al., (2019) where VDR acts as a prognostic factor in reducing the risk of death from breast cancer by inhibiting the proliferation of cancer cells [16]. Further, Muralidhar et al., (2019) found that VDR is a positive prognostic factor for melanoma patients by inhibiting Wnt/β-catenin signaling and enhancing immune cell infiltration and has the potential to boost antitumor immunity [32], and O’Brien (2018) found that the content of CpGs in VDR affects the risk of breast cancer by interacting with 25(OH)D.

1. **Conclusion**

 This systematic review provides an overview of the important role of VDR in reducing the risk of infection by killing bacteria and viruses, especially in the intestine, controlling gastrointestinal homeostasis, as an anti-inflammatory and anti-proliferative agent, and acting as a prognostic factor. VDR is expected to reduce the infection rate which is an indicator of improving the quality of nursing services.

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 **Table. 1 Grid Synthesis of VDR Role Description**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **No** | **Researcher & Research Location** | **Research Design** | **Objectives** | **Sample Size** | **Result** |
| 1 | (Febriza et al., 2020)/ Makassar, Indonesia | Experimental in vivo | To determine the levels of IL-6, TNF-α, and VDR in suppressing bacterial growth in the peritoneal fluid of male mice S. Typhi BALB/c strain | This experiment examined 30 mice divided into 3 groups of 10 mice each. Groups A and B were inoculated intraperitoneally with S. Typhi strain Thy1 and group C as control was not inoculated with S. Typhi. | VDR, IL-6, and TNF-α play an important role in killing bacteria. From the results of this research, IL-6 levels are related to the number of bacterial colonies. The lower the IL-6 level, the smaller the number of bacterial colonies. Similarly, TNF-α levels were positively correlated with the number of bacterial colonies. While VDR levels are also related to the number of bacterial colonies, the higher the VDR levels, the fewer the number of bacterial colonies. |
| 2 | (H. O. U. Yu et al., 2022)/Haikou, China | Systematic Review | To determine the relationship between Vitamin D / Vit D receptors, autophagy and infection | The sample was 10 studies obtained from 5 databases | VDR can inhibit TNF/NF-κB and IFN-γ signalling pathways and reduce the production of pro-inflammatory cytokines such as IL-6. VD can also inhibit renin gene expression through the VDR pathway thereby regulating the activity of the renin-angiotensin-aldosterone system and repairing ARDS caused by LPS. |
| 3 | (Zhao et al., 2018)/ Shanxi, China | Cohort Study | To elucidate the molecular mechanisms of epithelial VDR reduction in OLP and explore how oral epithelial VD-VDR signalling inhibits OLP initiation or progression | In this study, 14 people were identified with an age range of 28-66 years old and dominated by buccal mucosal sites | Evidence is convincing that lipopolysaccharides (LPS) decrease the regulation of VDR expression in oral mucosal epithelium dependent on TNFα-miR346 signalling. Vitamin D/VDR can suppress LPS-induced keratinocyte apoptosis by regulating the NF-κB pathway. Thus, vitamin D/VDR plays a protective role in the integrity of the oral mucosal barrier to overcome bacterial challenges, stopping or delaying the progression of Oral Lichen Planus (OLP). |
| 4 | (Sun & Zhang, 2022)/ Chicago, AS | Systematic Review | To assess the effect of vitamin D receptors on intestinal barriers in health and disease | Searches were conducted on PubMed and Google Scholar using the keywords vitamin D, VDR, tight junction, cancer, inflammation, and infection. | VDR is essential in regulating intestinal homeostasis by preventing the invasion of pathogenic bacteria, inhibiting inflammation, and maintaining barrier function |
| 5 | (Huss et al., 2019)/ Lund, Sweden | Meta-analysis | To investigate whether VDR expression in invasive breast tumor is related to breast cancer prognosis. | Samples were obtained as many as 718 women with invasive breast tumor with double imputation through analysis of tumor size, lymph node status, histological type, and molecular subtype. | The results showed that high expression of VDR in invasive breast tumor became a positive prognostic factor that was beneficial and reduced the risk of death from breast cancer. Women with VDR-positive breast tumor have better breast cancer-specific survival compared to women with VDR-negative tumor. |
| 6 | (Wardani et al., 2021)/ Makassar, Indonesia | Cross-sectional | To test the difference and correlation of vitamin D receptor levels and HMGB1 protein in HIV patients with mild and severe immunodeficiency and healthy control participants. | Three groups of 39 study subjects consisted of 13 participants of HIV patients with severe immune deficiency (SID), 13 participants of HIV patients with mild immune deficiency (MID), and 13 healthy controls (HC) with an average age of 34.5 years old. | VDR has a strong immunomodulatory effect and antimicrobial effect on HIV infection. The strong and significant negative correlation between vitamin D receptors and HMGB1 levels and immune status of HIV patients supports the important role of vitamin D receptors in immune status and severity of inflammatory processes in HIV-infected patients |
| 7 | (Jolliffe et al., 2018)/ London, UK | Cohort Study | To find out the effect of vitamin D receptor genotype on the risk of upper respiratory tract infections | 725 participants were studied. They ranged in age from 16 to 94, with an average of 59·7 (up to 15·0) years, and 54% were female. Overall, 67% of participants had respiratory comorbidities (34% asthma; 33% COPD). | Polymorphisms in VDR are independently associated with susceptibility to Upper Respiratory Tract Infections in adults and children. VDR mediates protection against respiratory infections by supporting antiviral responses |
| 8 | (Abdel-Mohsen et al., 2018), Cairo, Egypt | Cross-sectional | To investigate the interaction between autophagy and apoptosis and to investigate the relationship between autophagy and apoptosis and vitamin D and its receptors in hepatitis C virus (HCV) infection and its implications in progression to hepatocellular carcinoma | The sample of 90 patients was divided into 3 groups: Group I were healthy subjects (HS) consisting of 30 apparently healthy subjects with no history of malignant disease, group II (HCV patients) consisting of 30 HCV-infected patients (positive for anti-HCV Abs and HCV-RNA); and group III (HCV-HCC patients) consisting of 30 HCC patients above HCV (positive for anti-HCV Abs and HCV-RNA) | VDR plays an important role in vitamin D regulation in autophagy and apoptosis during HCV. VRD works as an anti-inflammatory, antiproliferative, and antitumor genesis. In addition, the results of this study show the important role of VDR in biochemical processes and have a strong positive correlation with biomarkers of autophagy, LC3, and apoptosis. |
| 9 | (M. Yu et al., 2021)/ Shanghai, China | Meta-analysis | To find out the effect of VDR on the pathogenesis of intestinal fibrosis | 19 intestinal tissue samples from Crohn's disease (CD) patients with colonic tissue from stenotic areas and non-stenotic control areas from the same patients with CDs | Research shows that VDR significantly alleviates CD-induced intestinal fibrosis by inhibiting fibroblast activation, maintaining epithelial mitochondrial function, and reducing EMT processes, demonstrating the key role of this protein in positively regulating intestinal fibrosis. |
| 10 | (Guzeeva et al., 2019)/ Moscow, Russia | Cross-sectional | To study 25(OH)-vitamin D levels, vitamin D receptor gene polymorphisms and bone metabolism in adolescents with chronic gastroduodenitis in helicobacter pylori (HP) infection-dependent. | The sample was 51 adolescents aged 12 to 15 years old. Group 1 contained 19 patients with helicobacter pylori (HP) infection and another 32 children without HP infection were put into group 2 | In adolescents with chronic gastroduodenitis, bone metabolism and 25(OH)-vitamin D levels are linked to the VDR genetic polymorphism gene, and the presence of Helicobacter Pylori infection. VDR levels help kill and lower infections due to Helicobacter Pylori and increase bone density. |
| 11 | O’Brieen et al., | Cohort Study | study the relationship between serum vitamin D, DNA methylation, and breast cancer | there were 1,070 cases, out of which 1,227 were found in white women who are at risk of breast cancer. | The concentration of 25(OH)D is associated with DNA methylation of CpGs in several vitamin D-related genes, with potential associations with genes related to immune function. CpGs methylation in genes associated with vitamin D may interact with 25(OH)D to influence breast cancer risk. |