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Review on Generation and Maintenance of Immunological Memory

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Abstract: Immunological memory is the phenomenon where by B and T cells have the unique ability to respond with heightened kinetics and efficacy to subsequent encounter with antigen relative to the initial exposure. It is the special characteristics of adaptive immune response which is the base for vaccination strategies. T and B cells are the groups of lymphocyte that are participated in immune memory by providing cellular and humoral mediated immunity respectively. Memory T cells are also sub-grouped into: effectors memory T cell and central memory T cell depending on their homing characteristics and effectors functions. Generation of immunological memory involves contact with pathogen of specific antigens, whereas their maintenance does not depend only on the presence of antigen, rather it relay on the production of exogenous cytokines. Antigen presenting cells have critical role in the activation and maintenance of memory T cell among them B cell is the most important one. Immunological memories are affected by different factors including age, nutrition and some others.

Key words: B cells · Immunological memory · T cells

INTRODUCTION

The body is protected from infectious agents and other harmful substances by a variety of cells and molecules that make up the immune system. Immunity is the ability of the body to tolerate the presence of material indigenous to the body (self) and to eliminate foreign (non-self) material. The primary function of the immune system is to prevent or limit infections caused by microorganisms [1].

Living organisms have both an innate immune system and an adaptive immune system. The innate immune system responds to pathogenic invasion immediately, fighting to destroy the infection without any prior "experience" with that pathogen. The adaptive immune system may take 4 to 7 days to take effect. In the adaptive immune system, specific antibodies (Ig) are produced against specific pathogens that provide life-long protective immunity to re-infection by that same pathogen. Lymphocytes belong to the adaptive immune system. Lymphocytes that are produced in the bone marrow but mature in the thymus are called T-lymphocytes. Like the macrophages, they are able to produce cytokines to create an inflammatory state and activate macrophages and B-lymphocytes. Lymphocytes that mature in the bone marrow are called B-lymphocytes and they produce antibodies [2].

Adaptive immunity plays a critical role at later stages of infection and responses to vaccination that include the generation of Ab responses, induction of Ag-specific cells, discriminating between 'self' and 'non-self' antigens and recruitment of immune cells to the site of infection or challenge. This leads to the killing of infected cells and/or clearance of the Ag and importantly also the development of specific immunological memory. The two main cellular components of the adaptive immunity, the B and T cells are responsible for the generation of humoral and cellular immunity, respectively [3].

Specific (or adaptive) immunity is enabled by a subset of white blood cell called lymphocytes. These come in two varieties -T lymphocytes, responsible for cell mediated immunity and B-lymphocytes which make antibodies. Immunological memory is generated by antigen- (pathogen-) driven expansion of those T and B lymphocytes that carry on their surfaces receptor proteins that bind specifically to the stimulating antigen. Cells possessing identical antigen receptors are collectively termed a clone. T lymphocytes are further subdivided into

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T helper cells and cytotoxic T cells that are distinguished by expression of the surface markers known as CD4 and CD8 respectively. We shall denote the totality of memory cells of each type as the CD4 and CD8 memory pools [4].

Immunological memory is the ability to raise a faster, stronger and qualitatively better immune response upon re-exposure to an antigen compared with that seen after the initial encounter with the antigen [5]. It is the characteristics of the immune system, can benefit the host by initiating a rapid and more effective immune response against invading pathogens, but it can also damage host tissues by mediating inflammation in response to allergens [6].

Generation of memory cells requires exposure to a pathogen that stimulates the cells in specific naive lineages and cross-reactive memory lineages. Stimulated naive cells expand in numbers, some die and others differentiate into memory cells. This encompasses the expansion and contraction phases of the immune response following acute infections [7].

Immunological memory is divided into cell and antibody mediated branches. The main players of these branches are T and B cells, respectively. Memory cell populations are maintained for many years sometimes leading to life-long immunity [8, 9]. Although adaptive immune cells has special ability to remember the previous pathogen encounter and response to them more rapidly than first one due to immune memory cells, there exists lack of information about the generation and maintenance of these memory cells and their underlying mechanisms. Therefore, the objectives of this paper were to provide a review on generation and maintenance of immunological memory as well as to describe the cells involved in immunological memory.

Concept of Immunological Memory

Definition: Immunological memory is the ability of the immune system to recall an encounter with a specific antigen and to mount a quantitatively and qualitatively superior secondary immune response on re-encountering the antigen, a process that involves the generation of memory T and B cells during the primary immune response [10]. It is the capacity of the immune system to respond faster and better (both in quality and quantity) to a secondary antigenic challenge than the first encounter with the same antigen. This rapid recall response can either completely prevent disease or greatly lessen the severity of clinical symptoms [11].

The ability of the immune system to ‘‘remember’’ previous encounters with pathogens and to respond with heightened kinetics and efficacy compared with the initial exposure, is a defining feature of the adaptive immune response of higher vertebrates [12].

Cells of Immunological Memory and Their Labor Division: Immunological memory is a defining hallmark of the adaptive immune response and can be manifested by antigen specific B cells and CD4 and CD8 T cells [13]. Memory cells confer immediate protection and generate secondary responses that are more rapid and of higher magnitude as compared to primary responses. Memory T and B cells are the progeny of antigen-specific naïve cells that have been clonally expanded in the course of an immune response and survive once antigen has been eliminated [14]. With regard to function, memory cells differ generally from naïve cells in being hyper-responsive to antigen and in synthesizing cytokines in large quantities [15, 16].

Both humoral and cellular immune responses comprise important arms of immunological memory and have evolved to perform distinct effector functions. The humoral immune responses include pre-existing antibody, memory B cells and long-lived plasma cells. The antibodies provide the first line of defense by neutralizing or opsonizing free extracellular pathogens. T cells (CD8 and CD4), by contrast, cannot recognize free pathogens, but instead identify infected cells and exert effector functions including direct cytotoxic effects on target cells and/or release of cytokines to inhibit growth or survival of the pathogen. CD4 T cells further provide help for antibody production and the generation and maintenance of CD8 T-cell memory [13].

The division of labor among the memory cells has implications for vaccination strategies because protection from infection or disease may rely primarily on either mechanism depending on the nature of the pathogen and the size and route of challenge. For instance, preformed antibodies and long-lived plasma cells are required to neutralize toxins or prevent infection by an incoming virus, whereas recall responses mediated by TCM cells and memory B cells may be sufficient to protect against viruses with long incubation time [17].

Memory B Cells: In the B cell system, immediate protection is mediated by long-lived plasma cells that are present in the bone marrow and secrete antibodies in an antigen-independent fashion, thus maintaining constant amounts in serum and body fluids [18]; recall responses

are mediated by memory B cells that rapidly proliferate and differentiate in response to antigenic stimulation generating a burst of plasma cells and a marked but transient elevation in serum antibodies. The contribution of B cells to immunological memory encompasses two distinct populations of cells that are generated during primary immune responses, long-lived plasma cells, which continue to secrete high levels of neutralising Ig for protracted periods of time well after Ag clearance and memory B cells, which can rapidly proliferate and differentiate into plasma cells following recurrent exposure to the initial immunizing Ag, there by simultaneously increasing the precursor frequency of Ag-specific memory B cells and enriching the pool of Ag-specific Ig [12].

Memory T Cells and Their Subsets: The same division of labor applies to the T cell system. Immediate protection is conferred by circulating or tissue-resident TEM that survey frontline barriers and diseased tissues for incoming pathogens and display immediate effector function upon antigen recognition; recall responses are mediated by central memory TCM that patrol the T cell areas of secondary lymphoid tissues where they can rapidly proliferate in response to antigens presented by DCs [19].

It has become increasingly recognized that memory T cells are heterogeneous in terms of both homing capacity and effector function. This heterogeneity is reflected in the current definition of TCM and effector memory T cell (TEMs). On the basis of their homing characteristics and effector function, two types of memory T cells have been distinguished in humans [20]. TCM express high levels of CCR7 and CD62L, molecules that are important for extravasation of T cells through the high endothelial venules and homing to the secondary lymphoid organs. In contrast, TEM do not express significant levels of these molecules and home preferentially to non-lymphoid tissue where they exert effector functions [21].

On the antigenic recall stimulation, TCM cells produce only IL-2 and do not make effector cytokines such as IFN-c. In contrast, tissue homing TEM cells produce copious amounts of effector cytokines (IL-4 and IFN-c) upon antigenic challenge and may constitutively express other cytotoxic effector molecules such as perforins and granzymes (CD8 cells). As in humans, several reports in mice have corroborated these findings and further suggest that the memory T cell pool is heterogeneous, containing cells with different migratory and effector capacities [22].

Generation of Immunological Memory Cells: Generation of immunological memory following contact with pathogens is antigen-specific and reflects a combination of humoral ('antibody') and cellular immunity, which is often lifelong [23].

Memory T Cells: Memory T cells arise from the expansion and differentiation of antigen-specific T cells upon interaction with their cognate antigen in the secondary lymphoid organs. They confer protective immunity in peripheral tissues and mediate recall responses in secondary lymphoid organs. To eliminate pathogens, primary immune responses have to be as intense as possible. Pathogens replicate rapidly and, to keep pace, antigen-specific T cells divide at a prodigious rate (as often as every six hours) and generate enormous numbers of effector cells [24].

These cells usually eliminate the pathogen, thus terminating the response. Effector cells are then redundant and most of these cells are destroyed en masse, presumably to provide 'space' for the subsequent responses of naïve T cells. Destruction of effector cells at the end of the primary response is a rapid and highly efficient process. Precisely how the cells are destroyed is not fully understood but is thought to be initiated by loss of contact with antigen: TCR stimulation ceases and leads to a decline in the production of life-sustaining cytokines. Deprived of these stimuli, T cells activate various intracellular death pathways and rapidly succumb to apoptosis [23].

Given that more than 90% of T cells participating in the primary response are rapidly destroyed, how do a small proportion of these cells survive to become long-lived memory cells? This question has been posed repeatedly over the past 50 years but is still largely unresolved. It is often tacitly assumed that generation of memory is an instructional process: most T cells are doomed to die at the end of the primary response and memory cells arise from a small subset of cells that have somehow learned to avoid death. In speculating on memory cell generation, it has to be borne in mind that, at least for CD8 cells, the fine specificity of T memory cells is established and fixed at the end of the primary response [25].

In order to provide efficient and effective protection, memory T cells must rapidly home to the lymph node draining the challenge site, proliferate and then migrate to the site of antigenic challenge in the periphery to mediate their effector function. This proliferation in the lymph node is important because the frequency of antigen-

specific T cells in the memory pool, although higher than naive cells, is not high enough to provide rapid protection against pathogens [26] (Sprent and Surh, 2002). Furthermore, pathogen-specific effector T cells may be short-lived and hence need to be continuously replenished from the memory T cell pool [27].

The quality and amount of memory T cells is set during antigen driven primary immune responses, which are initiated in the T cell areas of secondary lymphoid organs where rare antigen-specific naive T cells are stimulated by antigen presented by activated DCs. Pathogens can activate DCs by triggering multiple innate receptors either directly via PAMPs or indirectly via DAMPs leading to enhanced antigen presentation, co-stimulation and production of polarizing cytokines [28].

It is the nature and combination of the innate receptors triggered on DCs that determine their capacity to imprint different fates on proliferating T cells [29]. In response to certain viruses and intracellular pathogens, DCs produce interleukin-12 (IL-12), which promotes differentiation to T helper 1 cells capable of producing interferon-g, which is effective against such pathogens [30].

Likewise, in response to fungi or certain bacteria, Dcs and monocytes produce IL-1b, IL-6 and IL-23 that drive differentiation of Th17 cells that through secretion of IL-17 and recruitment of neutrophils mediate protection against extracellular pathogens [31]. The protective nature of these polarized responses is underlined by studies of human immunodeficiencies, where patients with defective Th1 or Th17 cell responses suffer from mycobacterial or fungal infections, respectively [32].

A more complex pathway triggered by helminths or allergens and involving epithelial cells and IL-4-producing innate or natural helper cells appears to control the induction of Th2 cells that produce IL-4, IL-5 and IL-13 and mediate protection or allergy [33]. Other effector (and memory) T helper cell subsets have been recently characterized in mice and humans, such as Th9 [34] and Th22 [35] cells, which may be involved in allergy and skin defense, respectively. CD4 T cells not only act directly to promote different types of inflammatory responses in tissues, but also play an essential role in B cell and CD8 T cell responses. A dedicated subset of follicular helper T cells is required for induction of germinal center reactions that leads to differentiation of memory B cells and long-lived plasma cells secreting high-affinity antibodies of switched isotypes [36]. Follicular helper T cells produce IL-21 and their differentiation is dependent on the transcription factor Bcl-6 [37] and a high-avidity interaction with antigen specific B cells [38, 39].

T helper cells can also promote DC maturation via CD40L-CD40 interaction and in this way help the generation of effector and memory CD8 T cells against poorly immunogenic antigens such as protein antigens [40]. The quality of the T cell response is profoundly influenced not only by the PAMPs and DAMPs but also by the nature of the DCs that present antigen and by the tissue microenvironment in which the T cell response takes place [41. Recent studies identified signaling pathways that appear to be involved in the differentiation of memory stem cells as well as drugs that favor the generation of TCM cell [42].

Memory B Cells: The B cell response to protein antigens is a highly orchestrated process that is initiated at the boundary between T and B cell areas where T cells primed by antigen-presenting DCs encounter specific B cells that have captured and processed native antigen relayed by macrophages lining the subcapsular sinus [44]. Thus, after initial contact with antigen, some of the B cells participating in the primary response form memory cells; generation of these cells is the end result of clonal expansion, differentiation and affinity maturation [45].

These 'primed' B cells are more efficient than naïve B cells and give heightened humoral responses on secondary contact with the antigen concerned.

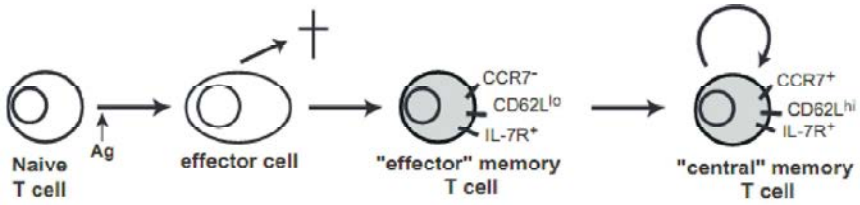

Fig. 1: Memory T cell differentiation. Naive T cells proliferate and differentiate into effector cells in the presence of antigen and costimulation. It appears that then IL-7Rhi subsets of effector cells differentiate to become memory T cells [43]

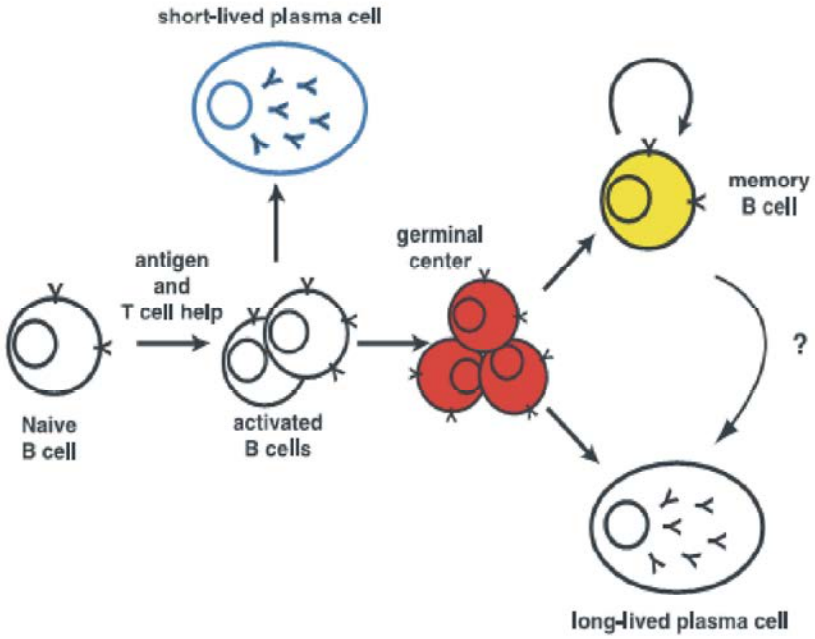

Fig. 2: Memory B cell and plasma cell differentiation [47]. The immune response is mediated by B cells, which use B cell receptors. After activation via their B cell receptor, B cells can differentiate quickly into short-lived plasma blasts producing a first burst of antibodies. Alternatively, B cells enter a germinal centre reaction, where they develop into high-affinity plasma cells or long-lived memory B cells, providing a lasting protection to the host by the production of neutralising antibodies [48].

Following antigenic stimulation, naive B cells undergo clonal expansion and form clusters of activated B cells known as extrafollicular foci. These activated B cells can either differentiate into short-lived plasma cells, or they can migrate back into the follicle and initiate a germinal center reaction. After proliferation and affinity maturation, germinal center B cells produce both long-lived plasma cells that produce high affinity antibodies and memory B cells that have high affinity B cell receptors [46]. The antigen-specific T-B cell interaction leads to a rapid expansion and differentiation of B cells into infection or disease may rely primarily on either mechanism depending on the nature of the pathogen and the size and route of challenge. For instance, preformed antibodies and long-lived plasma cells are required to neutralize toxins or prevent infection by an incoming virus, whereas recall responses mediated by TCM cells and memory B cells may be sufficient to protect against viruses with long incubation time [17].

Maintenance of Memory Cells: There has been much debate on the role of antigen in maintaining memory but it is now clear from carefully done cell transfer experiments employing a variety of model systems that both memory T and B cells can persist in the absence of antigen [49]. These findings were further extended by showing that memory T cells can persist even in the absence of the restricting MHC molecules [50].

Interestingly, sustained high amounts of soluble antigens can often lead to induction of tolerance or exhaustion both in T and B cells. In the case of certain chronic viral infections, antigen-specific T and B cells express a variety of inhibitory receptors that result in functional exhaustion of these cells [51].

Memory T and B cells as well as long-lived plasma cells can be maintained at relatively constant numbers in the absence of the eliciting antigen for virtually a lifetime. Their survival is dependent on exogenous cytokines that are available in distinct niches and determine the size of the memory pool. For CD4 and CD8 memory T cells, the survival cytokines are IL-7 and IL-15, which maintain these cells in a state of slow but continuous proliferation [52].

Memory B cells also divide at low rate but a survival cytokine has not yet been defined although it has been shown that an intact B cell receptor and phospholipase Cg2 are required for their long-term maintenance and function [53]. In contrast, long-lived plasma cells survive

without dividing in bone marrow niches organized by stromal cells that provide, in association with other cells, survival cytokines such as IL-6 and APRIL [18].

Unlike memory T cells that elaborate their cytokines only in response to antigenic stimulation, long-lived plasma cells continually produce antibodies, thus maintaining serum levels constant. The bone marrow also contains memory CD4 and CD8 T cells that may recirculate, as well as a recently described population of sessile resting memory T cells that occupies a distinct niche in contact with IL-7-producing stromal cells [54].

The fact that terminally differentiated effector memory cells such as TEM and plasma cells have reduced or no proliferative and reconstitution capacity led to the hypothesis that long term maintenance of memory cells would be dependent on cells that retain proliferative capacity, such as TCM and memory B cells or even on a specialized subset of ‘‘memory stem cells’’ [55]. In the case of T cells, this model is supported by the findings that long-term reconstitution capacity is characteristic of TCM rather than Tem cells and by the prospective isolation of a putative memory stem cell [56].

The Role of B Cell in Maintaining T Cell Memory: Long-term CD4 and CD8 T cell memory is seen in many different antigenic systems under both natural and experimental situations [57]. The accelerated responses seen upon re-exposure to Ag are due to quantitative (increased precursor frequency) and qualitative changes in memory T cells [58] that are transmitted epigenetically through subsequent generations of cells. T cell memory is maintained by the cytokines IL-7 and IL-15 through their positive effects on memory cell selection, survival and periodic homeostatic proliferation [59].

The particular interest is the role of Ag and B cells in maintaining long-term T cell memory. Ag-Ab complexes persisting on follicular dendritic cells have been implicated in sustaining T cell memory [60]. Since FDC do not process and present Ag efficiently, it has been postulated that B cells pick up this trapped Ag and present it to T cells; although lymphoid dendritic cells may also pick it up and present to T cells. Thus, B cells produce specific Ab needed for Ag deposition on FDC and they subsequently present the trapped Ag to T cells. Additionally, B cells provide co-stimulatory signals to T cells and are a source of cytokines that modulate T cell responses. B cell-expressed lymphotoxin and TNF, in particular, are essential for normal lymphoid organogenesis and development of FDC. Ag-Ab complexes persist for extended periods of time and a body of evidence indicates that exogenous Ags can be presented via cross-priming mechanisms to CD8 T cells; therefore, it was proposed that CD8 memory would be affected by the presence or absence of B cells and Ab. However, B cell-deficient mice maintain CD8 memory as well as wild-type mice and it has become clear from these studies and others that CD8 memory can be maintained not only in the absence of specific Ags [61] but also in the absence of cross-reactive Ags and MHC class I [62].

Factors That Affect Immune Memory

Aging: Normal aging has a marked effect on immunity, with the cumulative evidence indicating that cell-mediated immunity consistently shows age related decrements in function. The primary change in cell mediated immunity with aging in adult is a marked decrease in naïve T cells and increase in memory T cells. A decrease in naïve T cell of cell mediated immune response is associated with decreased production of IL-2 and high affinity IL-2 receptors and a reduced T cell proliferative response to novel antigen. However, an age related increase in memory T cell of Th2 responses increases production and secretion of IL-10 which, in turn, can inhibit the production and release of IL-12 and interferon, thereby suppressing the cellular inflammatory responses [63].

However, it is clear that any age-associated alterations in T cell responses may be due not only to changes in the T cells themselves but also to changes in APC required for their activation. Less is known about such age-associated changes and even less about alterations in the activity of the innate immune system, which is in turn required, among other things, for the activation of the APC and hence the adaptive immune system [64].

The naïve humoral immune responses also decrease with age: B cells show impaired activation and proliferation and antibody production is decreased in quality and quantity. Diminished CD4 T cell support for B cell activation and differentiation is thought to be largely responsible for an age related decline in antibody production to antigen [65].

Nutrition: The immune system has two interconnected arms, innate and acquired immunity, both of which interact with each other to generate protective immunity to the organism. Such response in essence requires, activation and propagation of immune cells and synthesis of molecules requiring DNA replication, RNA expression and protein synthesis and secretion, all of which consuming considerable anabolic energy. Energy cost of

immunity impairs the fitness of an organism [66]. Hence, immune competence is depending on nutritional status and can be easily dysregulated in state of imbalanced nutrition such as under nutrition and over nutrition (obesity) [67].

Obesity: Obese subjects showed either increased or decreased total lymphocytes in peripheral blood population and had decreased CD8 T cell population along with increased or decreased CD4 T cell. Obese subjects also showed reduced lymphocyte proliferation response to mitogen stimulation and dysregulated cytokine expression [68]. Obese animals show marked thymic atrophy, lower splenic and circulating T cells, decrease in mitogen stimulated lymphocyte proliferation capacity and cell mediated cytotoxicity [69].

Calcium: In addition to calcium's critical role in muscle function, it also plays an essential role in intracellular signaling. In immune cells, intracellular calcium regulates many cellular functions including: cytokine production, cytokine receptor expression and cell proliferation. Recently it has been shown that stimulated peripheral mononuclear cells from hypocalcemic cows have a muted intracellular calcium response compared to cows with normal blood calcium levels. Furthermore, when stimulated peripheral mononuclear cells from hypocalcemic cows were compared with stimulated peripheral mononuclear cells obtained from the same cows after intravenous treatment with a calcium solution, a muted intracellular calcium response was demonstrated only when the animals were hypocalcemic [70].

CONCLUSION

The hallmark of the immune system is that secondary responses to infectious agents are generally much more vigorous than primary responses this is due to immune memory. The immune memory is special future of adaptive immune response which is base for vaccination. Immunological memory is performed by special type of leukocyte known as lymphocyte. This lymphocyte has two classes of cells participated in immunological memory. Those are B and T cells that are involved in humoral and cellular immunity respectively. However, generation of this immunological memory requires contact with pathogens to generate antigen-specific and reflects a combination of humoral ('antibody') and cellular immunity, which is often lifelong, but the persistence of the generated memory cell does not depend on the presence of antigen. The immune memory can be affected by many factors. Therefore, based on above points the following recommendations are forwarded:

- Programmed vaccination should be experienced to generate immune memory
- Balanced diet should be provided to generate long last immunological memory
- Awareness should be created on the importance of vaccination in prevention of different infectious diseases

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