Photochemical & Photobiological Sciences

PERSPECTIVE

View Article Online
View Journal

Cite this: DOI: 10.1039/c6pp00355a

The role of UV radiation and vitamin D in the seasonality and outcomes of infectious disease

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The seasonality of infectious disease outbreaks suggests that environmental conditions have a significant effect on disease risk. One of the major environmental factors that can affect this is solar radiation, primarily acting through ultraviolet radiation (UVR), and its subsequent control of vitamin D production. Here we show how UVR and vitamin D, which are modified by latitude and season, can affect host and pathogen fitness and relate them to the outcomes of bacterial, viral and vector-borne infections. We conducted a thorough comparison of the molecular and cellular mechanisms of action of UVR and vitamin D on pathogen fitness and host immunity and related these to the effects observed in animal models and clinical trials to understand their independent and complementary effects on infectious disease outcome. UVR and vitamin D share common pathways of innate immune activation primarily *via* antimicrobial peptide production, and adaptive immune suppression. Whilst UVR can induce vitamin D-independent effects in the skin, such as the generation of photoproducts activating interferon signaling, vitamin D has a larger systemic effect due to its autocrine and paracrine modulation of cellular responses in a range of tissues. However, the seasonal patterns in infectious disease prevalence are not solely driven by variation in UVR and vitamin D levels across latitudes. Vector-borne pathogens show a strong seasonality of infection correlated to climatic conditions favoring their replication. Conversely, pathogens, such as influenza A virus, *Mycobacterium tuberculosis* and human immunodeficiency virus type 1, have strong evidence to support their interaction with vitamin D. Thus, UVR has both vitamin D-dependent and independent effects on infectious diseases; these effects vary depending on the pathogen of interest and the effects can be complementary or antagonistic.

Received 27th September 2016,
Accepted 14th December 2016

DOI: 10.1039/c6pp00355a

www.rsc.org/pps

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Background

Seasonality of infectious disease outbreaks has been noted for millennia. This is characterised by a consistent surge in the occurrence or manifestation of infection at different times of

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the year. The influenza vaccination is given in winter to prevent seasonal outbreaks, tuberculosis (TB) cases increase during and after winter, septicemia usually caused by *Staphylococcus aureus* is higher in winter, campylobacter rates increase in spring, while typhoid, malaria, cholera and dengue fever are more common in summer.[1–4] Each of these observations has been linked to a variety of social and environmental determinants, including climate, latitude, pathogen fitness, vector fitness, social behaviour, and variation in UV radiation (UVR). The latter is linked to a variety of determinants: latitude, temperature, clothing use, melatonin and most recently receiving a great deal of attention due to its role in modulating innate and adaptive immunity vitamin D. The interrelationship of each of these determinants on pathogen fitness and disease risk confounds the ability to identify the effect of each independent variable on disease prevalence. Therefore, a careful investigation and comparison of the mechanisms of action of these variables is required to understand the independent and complementary effects of these risk factors.

Seasonal differences in disease presentation exist across latitudes; there are greater seasonal fluctuations at higher latitudes where there are temperate climates than in countries close to the equator, which have more tropical climates.[3,5] However, not only does UVR, climate and vitamin D synthesis potential vary by latitude but so does pathogen diversity and fitness.[6,7] Thus, the links to disease presentation can be due to two main causes: (1) pathogen abundance, diversity and fitness and (2) host behaviour and immunity.[5] To determine whether there is a direct relationship between UVR, vitamin D and infectious disease risk, we will examine each independently and then discuss the evidence which links UVR exposure directly to the effect of vitamin D on disease prevalence and outcome.

UVR and vitamin D production

Solar radiation that reaches the earth's surface consists of UV (280–400 nm), visible (400–700 nm) and near infrared radiations (700–1000 nm). Although UV has less penetrance, it is associated with more health effects than the other two. Solar zenith angle (the difference between the theoretical perpendicular position of the sun and the incoming rays of the sun) influences UVR at the surface. This angle varies by season, latitude, and the time of day, according to where on the earth you are. There is greater variation in solar zenith angle at higher latitudes further from the equator due to the tilt of the earth, resulting in greater seasonal diversity at high latitudes compared to that at the equator. The amount of surface UVR is also modified by cloud cover, aerosols and atmospheric ozone.

The observed effects of UVR on immunity are primarily mediated through responses in the skin following local absorption. These effects are due to UVB (280–315 nm), which is only a small proportion (≈5%) of all UV reaching the earth and UVA (315–400 nm), the predominant UV hitting the earth (≈95% of the total UVR). Due to its shorter wavelength, UVB has a lower penetrance and its intensity varies more by season, latitude, altitude and the time of the day than UVA, which has relatively equal intensity during all daylight hours.[8]

Irradiation of the human skin with UVB starts the photochemical conversion of 7-dehydrocholesterol (7-DHC), alternatively called pro-vitamin D_3, into pre-vitamin D_3 and subsequently into vitamin D_3 (for a detailed review on vitamin D metabolism and UVB, see Engelsen *et al.*[9]). There is some evidence that a small amount of pre-vitamin D_3 can also form by UVA,[10] but the role of UVA in inducing or reducing vitamin D status is highly controversial. The majority of the cutaneous synthesis occurs in the epidermis where approximately 65% 7-DHC is present and it has the most UVB penetrance. A lower amount is produced in the dermis, approximately 35%, with 20% of UVB penetration. Vitamin D_3 is also obtained from dietary sources such as oily fish and its derived products like cod liver oil, while vitamin D_2 is obtained from plant sources, primarily fungus and yeast, and some nutritional supplements.

Within the first 10 minutes of exposure, 10–15% of 7-DHC is converted to pre-vitamin D_3 by absorption of UVR and this occurs at sub-erythermogenic UVB doses. Higher doses can lead to isomerization into other sterols such as tachysterol or lumisterol which affect the effective conversion to pre-vitamin D_3 and subsequently to vitamin D_3. Although tachysterol and luminsterol are considered biologically inactive they may have some biological function.[11] Thus, longer UVR exposures do not increase the vitamin D store. 50% of this pre-vitamin D_3 can isomerise to vitamin D_3 within 2.5 hours in the skin and is dependent on the concentration of pre-vitamin D_3 and the temperature (governed by the energy of the photon and exposure time). Vitamin D_3 for its activation needs two hydroxylation steps by CYP27A1 and CYP27B1, which primarily occur in the liver and kidney, respectively, to produce 25-hydroxy vitamin D [25(OH)D] and 1α,25-dihydroxy vitamin D [1,25(OH)2D] (Fig. 1). However, this can also occur in other cell types where vitamin D metabolites have autocrine function. This activated vitamin D_3 circulates in peripheral blood bound to vitamin D binding protein, with the concentration at a maximum 12–24 hours after exposure to UVB.

Pathogen diversity by latitude and season

Risk of infectious disease is directly related to the abundance and virulence of pathogens in the environment. Variance in pathogen infectivity is modified by numerous environmental conditions: latitude (which is associated with a changing climate and UVR), temperature, oxygen levels and humidity, land area and mammalian diversity all affect pathogen abundance, survival and virulence.[3,7] Thus, as UVR varies by latitude and season, which both independently impact the geographical and temporal distribution of pathogens, it is important to highlight these UVR-independent effects in order to delineate the UVR-dependent effects on seasonal infectious disease risk.

The favourable climate for pathogen fitness varies by pathogen type. Large seasonal changes in precipitation have the greatest association with pathogen species richness, while the temperature range only has a significant effect on bacteria, transmitted viruses and helminths.[6] Species of *Plasmodium*, *Vibrio cholerae*, *Legionella pneumophila* and dengue virus occur more frequently in the months of warm rainfall and humidity

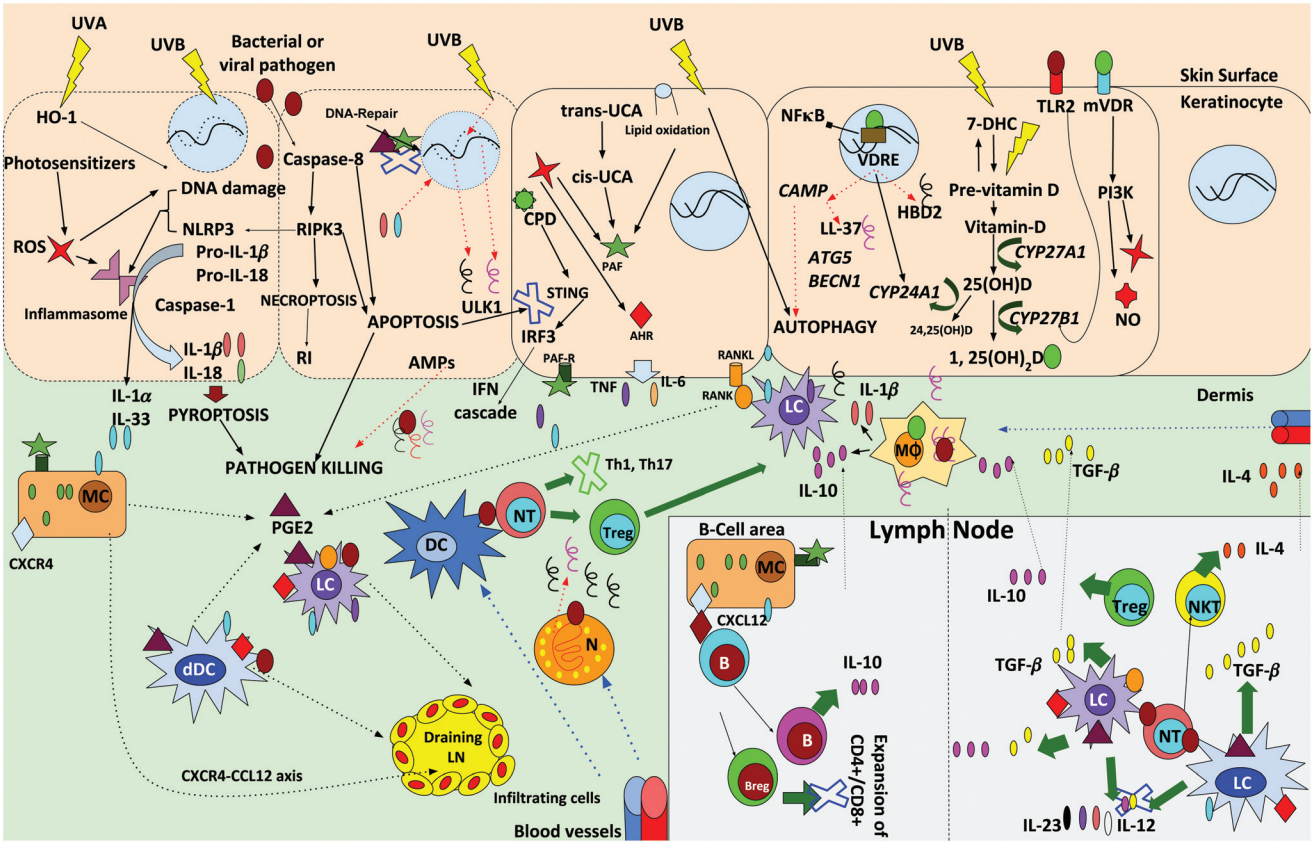

Fig. 1 Immune modulation by ultraviolet radiation (UVR) in the skin. UVR induces both innate and adaptive arms of immunity independent of and dependent on vitamin D production. The innate response is primarily mediated through the production of pro-inflammatory cytokines leading to inflammation, induction of cell death *via* various pathways (necroptosis, pyroptosis or apoptosis) and production of antimicrobial peptides (AMP). While adaptive immunity is T-cell mediated and is immunosuppressive. UVR absorption by chromophores (*e.g. trans*-UCA) leads to the activation of acute signaling pathways including platelet activating factor (PAF). PAF is generated by oxidization of membrane lipids of the keratinocytes, and signals *via* PAF receptor (R). Many cells express the PAF-R including monocytes, mast cells (MC) and keratinocytes. UVR generated reactive oxygen species (ROS) activates PAF production and cytoplasmic aryl hydrocarbon receptor (AHR), both of which signal *via* membrane-expressed epidermal growth factor, which leads to the release of Prostaglandin E_2 (PGE2). ROS can also activate inflammasome assembly leading to secretion of IL-1 family of cytokines. UVR-induced cyclobutane pyrimidine dimers (CPD) can stimulate STING (stimulator of interferon genes) leading to the activation of the interferon cascade, *via* interferon regulatory factor 3 (IRF3). Up-regulation of epidermal receptor activator of NF-κB-ligand (RANKL) *via* UVR induced PGE2 from keratinocytes leads to the activation of epidermal dendritic cells (DC).[270] These DC express RANK, the receptor for RANKL, and receptor activation results in the migration of these cells to the draining lymph nodes (dLN).[271] The effect of PAF, PGE2 and pro-inflammatory cytokines (TNF, IL-6 and IL-1β) enhances cell to cell communication and a change is the local cell population of the skin.[86] UVA can also induce the anti-oxidant heme oxygenase-1 (HO-1), which can be protective against UVB damage. The activated MC, dermal DC (dDC) and Langerhans cells (LC) migrate to the dLN in response to UV-induced-keratinocyte derived IL-33.[272] UV-induced keratinocyte-derived PAF activates up-regulation of the chemokine receptor CXCR4 on MC and induces the expression of CXCL12 (the ligand for CXCR4) in the B cells present in the dLN.[273] CXCL12 has chemoattractant properties and aids the activated CXCR4+ MC to migrate to the dLN.[274] There, these MC stimulate the IL-10 producing B cells (B) which mediate immunosuppression and down-regulate antibody secretion by interfering with B cell maturation by blocking germinal center formation, and T follicular helper cell function, hampering the generation of immunological memory to the presented antigen.[274,275] There, regulatory B cells (Breg) which respond to UVB inhibit the activation of immunity by DC.[276] LC and DC, the major APC of the epidermis, present antigens to naïve T-cells (NT) in the LN, which then differentiate and proliferate to give a population of activated, antigen-specific T-cells.[277] These LC and DC secrete high levels of TGF-β, and when they interact with T-cells, lead to the production of Foxp3+ regulatory T-cells (Tregs). These Tregs are cytotoxic for APC, are IL-10 producing and can suppress the function of other types of immunostimulatory T-cells.[278] LC cells that migrate to the LN in response to UVR can also activate Natural killer T (NKT) cells that secrete immunosuppressive cytokine IL-4.[279] Intracellular vitamin D is produced *via* a cascade of UVB induced metabolic steps and pathogen activation of TLR2 which up-regulates CYP27B1. Ligation of the active vitamin D metabolite (1α,25-dihydroxy-vitamin D [1,25$(OH)_2$D]) to the nuclear vitamin D receptor (VDR) which binds vitamin D response elements (VDRE) in gene promoters induce the production of AMP (LL-37, HBD2) and autophagy (*via* ATG5 and BECN1) or binding to the membrane VDR (mVDR) induces ROS and nitrogen oxide (NO), *via* phosphatidylinositol 3-kinase (PI3K). Red dotted lines pertain to everything that is related to AMPs. Black dotted lines indicate migration and secretion out of tissues and dotted blue lines indicate migration into tissues. Dashed cell boundaries for keratinocytes represent cells undergoing cell-death. Crosses represent inhibition of signaling or processes by UVR (blue) and vitamin D (green). Wherever a factor (secreted product, cytokine) is shown attached to a cell population, it simply indicates the importance of that factor in the cell's effector function. An attempt has been made to summarise major events; that does not imply that the things not depicted are not important, a further description is provided in the text. Abbreviations: N, neutrophil; Mϕ: macrophage; RI, reduced inflammation; ULK1, Unc51-like kinase 1.

which favour vector survival and pathogen replication within the vector,[12] while *Neisseria meningitides* favours dry conditions and thus it is more prevalent in cold dry northern winters and hot dry seasons in Sub-Saharan Africa.[3,13,14] *V. cholerae* is found to increase during times of excess rainfall and humidity, as its growth is favourable in warm water.[15,16] High temperatures favour pathogen replication, and influence the expression of virulence factors, from pathogens such as *Legionella*, *Shigella*, *Yersinia* and *Streptococcus*.[17–20]

The number of pathogen species decreases at higher latitudes; those furthest from the equator have less diversity, with tropical regions harbouring the greatest abundance of pathogens.[7] However, Murray *et al.*[6] found that after accounting for climate and other associated variables, latitude only had a significant association with the distribution of vector borne and parasitic diseases and this is likely due to the reliance on restricted reservoirs for transmission, limited by the environmental requirements favourable for vector survival. Bacterial infections were the only pathogen group for which mammalian diversity was not the driving force in geographical relatedness, with human population size being the greatest driver of similarity of bacterial infections between countries, suggesting that human-to-human transmission drives bacterial disease.[21] Thus, latitude alone has limited association with pathogen distribution, indicating that other factors are related to the seasonal spike in disease occurrence that is observed at varying latitudes.

Seasonal host–pathogen interactions

In addition to seasonal variation in UVR exposure according to latitude, there are also other seasonal environmental effects on the host's susceptibility to infection; climatic conditions, such as relative humidity and temperature, can alter the mucocilliary function,[22] which is the primary mode of viral and bacterial infection, modifying susceptibility to disease. Various social risks of disease transmission also vary by latitude, including human travel, public health spending, population size, as well as the behavioural practices which are associated with temperature changes, including sociability, participating in seasonal festivities increasing transmission likelihood, crowding, extent of clothing (thus UVR exposure), physical activity and time spent outside (in fresh or polluted air).[3,6,7,21] Therefore, there are multiple confounding effects of environmental and social risk factors that are associated with seasonal presentation of disease. However, different infectious diseases have different seasonal patterns of increased risk, some with a greater link to climatic variation than others.[3] Understanding these patterns, and relating them to the seasonal oscillation in immunity, may provide a clue as to which seasonal diseases may be linked to vitamin D and which to other aspects of UVR exposure or climatic variation.

Seasonal viral infections

Seasonality is one of the defining factors of influenza; however, this pattern of occurrence is much stronger at high latitudes and is weak equatorially. Due to the association with latitude, vitamin D has been investigated as a driver of flu seasonality.[23–25] In a large cohort of British adults vitamin D levels were found to have an inverse linear relationship with seasonal respiratory tract infections (high infection rate with low vitamin D levels) and a positive correlation with lung function.[26]

There is less seasonal association with the occurrence of flu pandemics, however, within these pandemics, mortality is seasonal and appears to be inversely proportion to UVR, again with greater association in temperate countries at higher latitudes, where UVR cycles are the greatest.[24] Peaks of mortality in the Spanish, Asian and Hong Kong flu pandemics occurred in periods of low UVB in Europe and the Americas.[27,28] Conversely, in Singapore (latitude 1°N), there were only small peaks in June and from December to January, periods of lowest vitamin D due to rain and cloud cover.[29] This humid climate is, however, favourable for virus transmission and the timing coincides with the peak tourism period, thus increasing the chance of transmission and an influx of infected individuals from higher latitudes.[24,30]

In subtropical regions, such as Japan and Hong Kong (23–26°N) there are observed winter peaks in influenza and very small summer peaks, despite relatively high vitamin D levels throughout the year.[31] However, there are still small decreases in winter vitamin D levels in these regions and thus susceptibility to disease may be more related to changes in vitamin D levels, rather than a threshold effect. As such the largest winter incidence occurs in high latitudes (60–70°N) where the change in seasonal vitamin D is the greatest.[24,32] Furthermore, when live influenza vaccine is given to volunteers in winter it leads to greater febrile reaction and increased antibody titres, compared to those who receive it in summer.[33,34]

Similarly to flu, there is also wintertime seasonality observed for other viruses, including gastroenteritis-causing rotavirus and respiratory syncytial virus (RSV).[35–37] Again, these have greater seasonal peaks in temperature regions, some of which also show spring and autumn peaks,[38] and less seasonality circulating year round in the tropics, but still showing some seasonal timing of peak instances even in the lower latitude. The immune response to human immunodeficiency virus type 1 (HIV-1) has also been shown to be season dependent, with infected individuals having lower levels of CD4+ T cells and lower mean CD4+/CD8+ ratios during summer and spring; however no effect on viral load has been seen and these effects are more pronounced with the increasing age of the subject.[39]

Conversely to the high winter prevalence of respiratory viruses, many childhood viruses show summer time peaks in incidence including varicella zoster virus (which causes chicken pox), paramyxovirus (which causes measles), the mumps virus, and enteroviruses, such as poliovirus.[2] It has been suggested that there is no direct climatic link between epidemics of these diseases which are strongly influenced by vaccination programmes and highly increased during school terms.[2] However, these summertime peaks are also more

common in temperate climates and there is a loss of summertime seasonality of polio epidemics closer to the equator, suggesting that there may be a latitude link to disease risk associated with UVB exposure, but there is limited evidence for a link to vitamin D.

Seasonal bacterial infections

The incidence rate of TB oscillates seasonally in many parts of the world, particularly at high latitudes,[1,40–42] the lowest rates generally occurring in the quartile following summer, when vitamin D levels are highest. We also have evidence that the winter increase in TB cases is greater in HIV-infected individuals (Coussens AK, Oni T *et al.*, unpublished). Vitamin D deficiency is common in TB patients,[1,43] and in latently infected individuals who progress to active TB.[44] The lower vitamin D status of TB patients is further exacerbated by co-infection with HIV-1,[1] suggesting a very strong interaction between vitamin D and the seasonality of TB incidence in this population.

A systematic review of 11 studies conducted across Africa, Asia, the Middle East and Europe found that the most predominant peak in TB rates actually occurred in summer and spring, and suggested that due to the lag phase from infection to disease, there is a peak in winter infections and that disease manifests 6 months later.[45] These finding highlight the fact that for chronic infections the seasonality of incidence must take into account the factors driving transmission and disease progression.

Meningococcal meningitis is another aerosol-transmitted disease with high seasonality; it occurs in dry seasons and declines in periods of rain.[46] Converse to the hot-dry peaks in Africa, there are wintertime peaks of meningococcal meningitis in North America and Europe, which are associated with the low humidity of northern hemisphere winters.[13,46,47] The strong association with seasonal humidity, which varies across latitude, suggests that there is little association with vitamin D and meningococcal disease.

Seasonality is also very strong for cholera and also non-cholera diarrhoeal diseases.[2] These increase during the rainy season, are favoured by warmer climates, and show a strong seasonal pattern at higher latitudes, with less seasonality closer to the equator.[48,49] However, it appears that this seasonality is linked predominantly to changes in the aquatic environment in which *V. cholerae* persists, including the availability of phytoplankton, which act as reservoirs for the bacteria.[50] There is little association with UVR, except for an increase in temperature favouring replication.

Seasonal vector-borne infections

Due the reliance of vector-borne disease on their host vector for transmission, malaria and dengue haemorrhagic fever have transmission rates which fluctuate seasonally with rainfall patterns, favouring mosquito activity. However, it has also been shown that climate is not the sole driver of outbreaks, for example female mosquitoes and seasons were strongly correlated with dengue cases.[51] It has also been shown for malaria that parasite density is associated with body temperature and age, with adults being able to clear the parasite more easily than children.[52–54] This indicates that there is also an immunological influence on the response to infection during peak transmission times, and there is evidence that vitamin D deficiency increases the severity of malarial disease.[55–57]

Seasonal immunity

The seasonal emergence of disease for many viral and bacterial infections has been linked to changes in cellular and humoral immunity in certain times of the year. However, it could also indicate either an increase in rates of infection, likely for acute infections like influenza, or an increase in symptom severity and loss of pathogen control, as could be the case in chronic infections, like TB.

In line with the fact that immunity oscillates seasonally, numerous studies have shown that peripheral blood responses of healthy individuals oscillate along the same continuum, showing seasonal changes in the frequency and function of various cell types which may lead to increased risk of disease. A longitudinal study of healthy individuals in The Netherlands showed a summer decrease in the percentage of monocytes (MN) expressing pattern recognition receptors (PRR) toll-like receptor (TLR) 2 and 4; decreased pro-inflammatory cytokine secretion (interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF), interferon-gamma (IFNγ) and IL-10) upon Lipopolysaccharide (LPS) stimulation; an increase in circulating CD4+ and CD8+ T cells, including naive CD4+CD45RA+ T cells; and a decrease in the proportion of circulating anti-inflammatory regulatory T cells (Tregs).[58,59] Similarly, we also found a winter decrease in circulating lymphocytes in two South African cohorts, and an increase in macrocytic anaemia in winter compared to summer, both of which were reversed by winter vitamin D supplementation.[60]

Further to the seasonal changes in the number of circulating cells in individuals in countries at high latitude, a recent study has shown reciprocal summer and winter fluctuations in whole genome expression patterns of circulating white blood cells and adipose tissue from populations in the southern and northern hemispheres.[61] These gene sets included pathways associated with circadian rhythm, driven by differences in sunlight, vitamin D signaling, and multiple hormone receptor pathways. They also showed that the pattern of circulating cell types changed seasonally and these were correlated to changes in gene expression. Moreover, the pattern of cell type fluctuation was completely different for individuals from The Gambia, an equatorial country, for whom the numbers of all seasonal cell types peaked during the rainy season, when exposure to season pathogens, such as *Plasmodium*, is greatest.

The seasonal change in immunity according to latitude is also observed in response to vaccination. Poliovirus vaccine produces higher antibody responses in temperate (high latitude) compared to tropical regions (low latitude),[62] while the bacillus Calmette-Guérin (BCG) vaccine shows a graded response and becomes more protective with increasing distance from the equator.[63] Vaccines against poliovirus,[64]

influenza virus,[34] hepatitis B virus,[65] and rubella virus[66] also show higher antibody response when administered in winter compared to summer.

For all of these seasonal and latitude associated observations for infectious disease prevalence and changes in immunity, it is possible that they are mediated by either direct effects of UVR on pathogen viability or indirectly *via* UVR generation of vitamin D and other immune modulatory compounds.

Variation in UVR and its link to infectious diseases

Direct effects of UVR on pathogens

Being a mutagen, UVR has been hailed as a selector of evolution and therefore geographical and seasonal diversity of pathogens can be modified by incident UVR.[67] UVR alone or in combination with certain chemicals successfully reduces the viability of pathogens in blood, including *Plasmodium* spp.,[68] *Leishmania donovani infantum*[69] and even ebola virus.[70] UVR is also effective in killing *Malassezia furfur*, a skin fungus,[71] *S. aureus* on the skin of dermatitis patients,[72] *Mycobacterium leprae* isolated from foot pads of mice[73] and clinical isolates of *M. tuberculosis*.[74] However, *M. tuberculosis* isolates have also shown evidence of recovery from UVB damage through DNA repair.[74]

UVR can also alter the richness of commensal bacteria (microbiome) on the skin, although different species vary in their tolerance to UVB.[75] Although commensal bacteria are not themselves pathogenic, disturbances in their individual abundance can shift the homeostatic balance towards an inflammatory phenotype and disease manifestation.[76]

Regulation of immune cell function by UVR

The basic cellular response to UVR is protective in nature and is directed towards combating the deleterious effect of UVR radiation on cellular function. In general, this coincides with activation of an inflammatory response in the skin that is polarised towards immune suppression/tolerance. Although erythremal doses of radiation are more effective in achieving systemic immunomodulation, suberythremal doses of UV can also induce local and systemic immunosuppression, in humans and mice.[77] Therefore, with limited evidence of photoadaptation (a reduction in immune response due to multiple exposures to UVR; see Norval *et al.*[78] for a review), daily suberythremal doses of UVR have the potential to contribute to our overall inflammatory milieu and consequently our response to invading pathogens.

The skin is the largest organ of the body and the skin architecture offers the first barrier of protection to invading pathogens and the environment (Fig. 1). The outermost layer, the epidermis, absorbs most of the UVR and is comprised mostly of keratinocytes, Langerhans cells (LC) (antigen-presenting cells [APC] of the skin), melanocytes,[79] and CD8+ T cells.[80] The second layer, the dermis, has a host of immune cells including macrophages, dendritic cells (DC), including dermal DC (dDC), plasmacytoid DC, T cells including CD4+ T helper (Th) cells (Th1, Th2, Th17), mast cells (MC), eosinophils, and neutrophils.[81] The lymphatics and vascular conduits allow migratory cells to traffic between the skin and vasculature.[82]

Chromophores in the skin including *trans*-urocanic acid (UCA),[83] DNA, RNA[84] and membrane phospholipids present in keratinocytes and APC,[85] tryptophan, 7-DHC[86] and elements in the complement pathway[87] undergo changes following absorption of UVB. High UV doses can lead to photodamage to DNA by UVB and UVA, giving rise to cyclobutane pyrimidine dimers (CPD), also called cyclic dinucleotides and 6-4 photoproducts.[88] The CPD released can stimulate STING (stimulator of interferon genes) leading to the activation of the interferon cascade, *via* interferon regulatory factor 3 (IRF3).[89]

UVB also generates aryl hydrocarbon receptor (AHR) ligands from tryptophan in the skin[90] and oxidises lipids and proteins in UV-exposed keratinocytes. In addition, UVA is absorbed by photosensitizers (endogenous chromophores such as flavins, porphyrins, and melanin) leading to the generation of reactive oxygen species (ROS), organic free radicals. All these changes following UVR absorption result in oxidative stress. However, at the same time, UVA can also induce the anti-oxidant heme oxygenase-1 (HO-1), which can be protective against UVB damage.[91]

UVR induced anti-microbial activity *via* inflammasome activation and cell death

UVR generated photoproducts (PP) such as *cis*-UCA, CPD and ROS can lead to the activation of a variety of innate immune responses (Fig. 1). Keratinocytes regulate homeostasis after UVR-induced PP generation by secreting abundant pro-inflammatory IL-1 family cytokines: IL-1α, IL-1β, IL-18 and IL-33. Proteolytic activation of the pro-form of these cytokines is dependent on UV-induced formation of the inflammasome complex, which mediates their caspase-1 processing, one of the earliest responses of keratinocytes to UV damage.[92] This abundance of IL-1 family mediators results in infiltration of cells, such as macrophages and neutrophils, and inflammation influencing the host response, both locally and systemically.[93]

At lower UV doses, to counter the effect of PP, homeostatic apoptosis (controlled cell death) occurs independent of the production of pro-inflammatory cytokines, resulting in immune tolerance.[94] With increasing UV dose, the damaged cells produce danger signals through "alarmins" such as IL-1α and IL-33 and pro-inflammatory cytokines such as IL-1β. These can lead to NRLP3 and caspase-1 mediated pyroptosis by the keratinocytes[95] or caspase-8 and RIPK3 mediated necroptosis. The latter can lead to the eradication of skin infections such as *S. aureus* by reducing inflammation and through the direct effect of RIPK3 on IL-1β and apoptosis induction.[96] Keratinocytes also suppress the replication and spread of vaccinia virus by undergoing rapid apoptosis, in a process requiring STAT3.[97] Skin keratinocytes exposed to low UV doses induce a Th1 response *via* induction of IL-18 and

activation of LC and DC, leading to the production of IFNγ and TNF. Increasing UVR doses on the skin activates an inflammatory reaction coordinated by Th17 cells and IL-1β secretion from keratinocytes, leading to secretion of IL-17A and IL-17F by LC and DC. At higher UV doses an anti-inflammatory tolerogenic state is induced by alarmin production from the keratinocytes promoting a Th2 polarized response in LC and DC. This leads to secretion of IL-10, IL-5 and IL-13 and activation of Prostaglandin E_2 (PGE_2) and anti-inflammatory T-regs secreting IL-10 and TGF-β.[93]

The IL-1 family pro-inflammatory cytokines aided by alarmins also activate nearby healthy cells to secrete antimicrobial peptides (AMP).[93] AMPs such as β-defensins (HBD2, HBD3), ribonucleases, psoriasin, dermicidin and cathelicidin (LL-37), which aid in direct killing of the pathogens, are secreted by keratinocytes, sebocytes, MC and infiltrating cells, such as neutrophils and Natural Killer (NK) cells.[98] Some AMP are constitutively expressed while others are induced upon infection,[99] skin barrier disruption[100] by sub-erythremal doses of UVR,[101,102] or by up-regulation of alarmins.[93] AMP serve as a link between the innate and the adaptive system as they act as both antimicrobials and chemoattractants for many effector cells, including neutrophils, MN and DC.[103,104] In turn the AMPs, particularly cathelicidin, also have "alarmin" functions where it can induce the production of other inflammatory mediators through a number of pathways including the production of IL-1β and inflammasome activation.[105,106]

UVR-induced immunosuppression and tolerance

The mechanism of UVR-induced immune suppression has been discussed in detail in many reviews.[86,107,108] This mechanism of immunosuppression has been gathered largely from animal models that have employed a variety of antigens to characterize the response after irradiation and the application of the antigen to the irradiated site (local immunosuppression) or a distant non-irradiated site (systemic immunosuppression). The consensus view and the detailed mechanism are summarized in Fig. 1. The end result of UVR exposure is significant suppression of immunity with inhibition of the expansion of the effector CD4+ and CD8+ T-cells in the skin draining LN (dLN) and impaired development of peripheral memory T-cells in the skin. Once generated, the immunosuppression is long lasting, leading to tolerance, such that if the same antigen is encountered in the future, the T cell response to it will be suppressed.[107]

In vivo studies of UVR exposure

Most animal models of UVR exposure have demonstrated its immunosuppressive effects,[109] resulting in increased microbial load for animals infected with *Mycobacterium bovis* BCG,[110,111] *Mycobacterium Lepraemurium*,[112] *Trichinella spiralis*,[113] *Listeria monocytogenes*[114] and cytomegalovirus[115] and an increase in mortality for those infected with *Plasmodium chabaudi*,[116] *C. albicans*,[110,117] herpes simplex virus type 1 (HSV),[118,119] and influenza virus.[120] This effect was often associated with a decrease in memory lymphocyte response including down-regulation of delayed type hypersensitivity (DTH) and immunoglobulin production in UV irradiated animals infected with *Borrelia burgdorferi*,[121] *Leishmania major*,[122] *Metarhizium anisopliae*,[123] reovirus[124] and murine leukemia virus.[125] UVR showed no effect against *Schistosoma mansoni*.[110,126]

While there has been extensive experimentation of UVR in animal models, there is a paucity of human data. What does exist shows that the severity of immunomodulation following UVR exposure is less intense than that in animals.[127] In humans, UVR mediated immunosuppression has been associated with reactivation of a latent infection (*i.e.* HSV),[128] an increase in severity of symptoms, a reduction in resistance to infection and an increase in the oncogenic potential of latent oncogenic viruses.

Due to the UVR-induced down-regulation of microbial specific effector T cells, decreased antibody production by stimulated B cells and low levels of DTH to tested common microbial antigens,[129] it has been suggested that UVR could reduce the efficacy of common vaccinations.[130] The notion is reinforced by the observation that immunity to measles virus weakens with high UVR[131] and a Th2 cytokine response is observed for measles and poliovirus.[132] It has been reported that the vaccine antibody response to hepatitis B surface antigens is weaker in people with polymorphism in the IL-1β gene[133] and a suppressed T cell response is seen in subjects with high *cis*-UCA.[134] Both of these factors promote UVR mediated immunosuppression.

Daily light cycling and melatonin

Diurnal changes in periods of light exposure also regulate melatonin secretion, primarily produced by the pineal gland. However, it is also made by cells in the bone marrow, thymus and lymphocytes, indicating that it can have extra pineal production, for autocrine action.[135,136] Melatonin has seasonal and diurnal cycles as the period of darkness increases: epitomised by low secretion in the day and high levels at night, which is exacerbated at high latitudes where the period of darkness is extended in winter.[137] It also decreases with increasing age, which may be associated with age-related immunocompromised status.[138]

Similar to the active vitamin D metabolite, $1,25(OH)_2D$, circulating melatonin has a short half-life of 20–40 min, such that tissue specific generation is vital to local function. Light cycles in winter and summer affect the peak height and length of duration of secretion of melatonin, with the greatest length of production in winter.[139] However, human studies investigating the seasonal changes have found peak levels occurring in autumn, where there is the greatest change in light cycle, with increasing length of darkness throughout the season.[140] Melatonin possesses anti-oxidant properties and can counteract the DNA damaging effect of UVB. However UVB also induces melatonin metabolism on keratinocytes, counteracting its protective effect.[141]

The action of melatonin on the immune system is mediated through MT_1 and MT_2 receptors, which are expressed on peripheral blood mononuclear cells (PBMC) and neutrophils and whose activation leads to a decrease in cyclic adenosine mono-

phosphate (cyclic-AMP) concentration.[142–145] The density and distribution of these receptors also vary with circadian time, contributing to their daily response cycle.[146] Melatonin also interacts with calmodulin, tubulin and RORα and RORγt transcription factors.[145,147] Through the latter, it promotes T cell maturation towards the Th17 axis, cells conditioned for IL-17 production, promoting neutrophil influx. Humans who receive 5 days of oral melatonin have circulating neutrophils with increased chemotactic potential and production of chemokines CXCL8, CCL2 and CCL3, while their PBMC have less chemotactic potential towards zymosan activated human serum. Conversely, if PBMC and neutrophils are exposed to melatonin *in vitro*, they both have increased migration towards zymosan activated human serum.[148]

Besides controlling and increasing CD4 T cell production, melatonin treatment of human MN increases the Th1 polarising cytokine IL-12, which enhances IFNγ production by Th1 cells and NK cell activity. Moreover, melatonin also promotes neutrophil and macrophage production of IL-4, IL-6 and GM-CSF. Together, this would suggest that the increased melatonin levels, associated with longer periods of darkness in winter, may prime the innate and adaptive immune responses to help prevent infection, allowing a quicker response to infection. However, in cases of underlying chronic infection this increased pro-inflammatory response may be detrimental when combined with winter-associated vitamin D deficiency and UVB exposure, which generally modulates an anti-inflammatory response, helping to control the inflammatory balance, preventing inflammation-associated morbidity.

Vitamin D association with infectious disease

Recent studies and meta-analyses have identified significant associations between lower serum 25(OH)D concentrations and increased rates of a variety of infectious diseases, including TB,[1,149] acute respiratory tract infections,[150] malaria[57] and HIV progression.[151] Polymorphisms in the vitamin D receptor (VDR) and other vitamin D-related genes have been associated with many bacterial and viral infections, including TB, HIV, dengue fever, hepatitis B and RSV.[43,152–156] A recent prospective study of TB incidence in HIV-1 infected individuals initiating antiretroviral (ARV) therapy identified a significant correlation between vitamin D deficiency and incidence of pulmonary TB, but not malaria or pneumonia.[157] Analysis of the same cohort also showed that vitamin D deficiency was significantly associated with increased all-cause mortality, compared to vitamin D sufficiency.[158] Conversely, other studies have shown no association between vitamin D deficiency and disease, including HIV-associated cryptococccal meningitis.[159]

These variable associations suggest that vitamin D may have significant effects on a selected group of infections, or the effect may vary depending on the location and genetic background of the population investigated. We have recently conducted a meta-analysis of all vitamin D related studies of infectious diseases in South Africa. We found that there was greater association between vitamin D deficiency or supplementation and disease presence or response to infection, when the study was conducted at locations at higher latitudes and lower altitudes, compared to those at lower latitudes and higher altitudes, where vitamin D sufficiency is greater.[160]

Pathogen effect on vitamin D metabolism

While vitamin D deficiency is associated with disease incidence and progression, vitamin D metabolism can also be modulated by infection. Stimulation of PRR (including TLRs) on the surface of immune cells and keratinocytes, particularly phagocytic cells designed to engulf invading pathogens, induces *CYP27B1* expression.[161,162] This accelerates intracellular 1,25$(OH)_2$D production which subsequently activates *CYP24A1* expression, the vitamin D 24-hydroxylase. Exacerbated by the fact that 1,25$(OH)_2$D has a 4–8 hour half-life compared to the 15–18 day half-life of its precursor metabolite 25(OH)D,[163,164] and that *CYP24A1* expression leads to vitamin D catabolism, concomitantly, induction of these enzymes by pathogens may lead to exhaustion of available circulating 25(OH)D if sufficient intake is not maintained (Fig. 1). Therefore, disease associated vitamin D deficiency, measured according to 25(OH)D levels, may be a direct result of the infection, rather than deficiency alone leading to increased susceptibility to infection. In fact, it is likely a compounding effect that pathogen induced-vitamin D deficiency favours the infection outcomes towards the benefit of the invading organism.

As such, many pathogens down-regulate VDR signaling. *Aspergillus fumigatus* secretes a toxin capable of down-regulating the VDR in macrophages,[165] Epstein-Barr virus (EBV) down-regulates VDR expression during B cell infection[166] and the H1N1 influenza virus down-regulates the VDR pathway in the lungs of multiple animal models of infection.[167] Conversely, infection with *M. tuberculosis* and *Plasmodium vivax* up-regulates VDR expression.[161,168]

Vitamin D regulation of immune cell function

Vitamin D differs from most vitamins in that its primary active metabolite 1,25$(OH)_2$D is a steroid hormone. Unlike most vitamins which act as antioxidants or enzyme co-factors, 1,25$(OH)_2$D functions by acting as a ligand for the VDR present in the cell membrane (mVDR) or the nucleus (nVDR). Binding to the mVDR elicits rapid responses through activating phosphatidylinositol 3-kinase (PI3K) signal induction. Conversely, 1,25$(OH)_2$D binding to the nVDR activates a ligand-dependent transcription factor complex when VDR is in a heterodimer with the retinoid X receptor (RXR). This VDR–RXR complex binds repeats of PuG(G/T)TCA, known as vitamin D response elements (VDREs), in the promoter of more than 900 genes and microRNA to regulate their expression,[169–171] and thus, by doing so, 1,25$(OH)_2$D becomes a master regulator of cell function (Fig. 1).

Since the discovery that MN and macrophages express a repertoire of vitamin D-regulated genes, further studies have made similar observations in a range of other cell types.

Activated T and B cells, DC, lung epithelial cells and skin keratinocytes all express VDR, *CYP27B1* and *CYP24A1*, indicating that they possess the machinery to utilise and generate 1,25$(OH)_2$D from 25(OH)D.[172–175] Mast cells express VDR and respond to 1,25$(OH)_2D_3$, but not 24,25-dihydroxy-vitamin D_3 (24,25$(OH)_2D_3$).[176] Furthermore, monocyte-derived macrophages (MDM) have high expression of the 25-hydroxylase enzyme CYP27A1, whereas MN and DC have only low expression. Accordingly, MDM were also found to be able to convert vitamin D_3 to 1,25$(OH)_2D_3$ with greater efficiency than DC.[177] It could be argued that lymphocytes activated *in vitro* do not represent the same population of cells which infiltrate the lung during pathological processes. However, the fact that they express both VDR and the enzymatic machinery capable of producing intracellular 1,25$(OH)_2$D indicates that they have the capacity to utilise circulating 25(OH)D when stimulated to do so and to respond to locally produced 1,25$(OH)_2$D. The capacity for all immune cells to generate intracellular 1,25$(OH)_2$D, through autonomous CYP27B1 production, suggests that the main action of vitamin D during an immune response is *via* nVDR modulating the transcriptional response of cells.

Anti-microbial effect of vitamin D

Vitamin D metabolites elicit antimicrobial effects through binding both mVDR and nVDR. The first mechanisms identified by which 1,25$(OH)_2D_3$ mediated innate cellular control of *M. tuberculosis* infection involved the induction of nitric oxide (NO), NAPDH-dependant oxidases, and phagolysosome fusion.[178–180] Vitamin D mediates its effect on the latter two functions *via* PI3K signaling through the mVDR. However, with the use of specific mVDR and nVDR inhibitors, it was shown that the predominant mechanism of vitamin D antimycobacterial activity is actually mediated *via* the nVDR.[181] Specifically, it is mediated *via* the activated VDR–RXR transcription factor complex inducing the expression of the cathelicidin antimicrobial peptide (CAMP) gene, having three VDRE in its promoter.[161,181,182] CAMP mRNA is translated into a propeptide hCAP18, which is further enzymatically cleaved by neutrophil proteinase 3 to produce the active antimicrobial agent, cathelicidin (LL-37).[183]

LL-37 is one of the AMPs which directly inhibit mycobacteria viability in liquid culture, although neutrophil-derived lipocalin (NGAL) and human neutrophil peptides 1–3 (HNP1–3, members of the α-defensin family) show greater potency for mycobacterial killing than LL-37.[184] AMPs, in general, are small peptides with a cationic charge that allows them to bind to negatively charged prokaryotic cellular membranes. Thus they have broad action against Gram-positive and Gram-negative bacteria, although each targets different bacteria with varying effects (reviewed by Diamond *et al.*[185]).

The bactericidal activity of cathelicidin is postulated to be *via* its ability to bind and puncture holes in the bacterial cell wall phosphatidylglycerol monolayers.[186] Similarly, LL-37 can damage the membrane of envelope and non-envelope bound viruses, including influenza A virus (IAV), smallpox-causing vaccinia virus, papillomavirus and RSV and, by doing so, decrease the virus binding and infection of cells.[187–190] Since their first identification in monocytic phagocytes, further studies have reported that neutrophils, T cells, B cell, NK cells, DC, MC and epithelial cells in the respiratory and intestinal tracts secrete AMP regulated by vitamin D.[191–193] Vitamin D metabolites therefore have the ability to induce antimicrobial activity in a diverse range of cells in response to bacterial and viral infection.

Cathelicidin is unique in that it not only has direct antimicrobial activity, but its pro-peptide, hCAP18, also induces autophagy through up-regulating the expression of beclin-1 (*BECN1*) and autophagy protein 5 (*ATG5*).[194] Autophagy has recently been identified as a key intracellular process to antagonise mycobacteria-mediated inhibition of phagosome maturation, a key mechanism by which mycobacteria subvert the innate immune response.[195] Autophagy also increases the production of bacterial degradation products in antigen presenting cells for PRR activation and presentation to the adaptive immune system.[196]

VDR activation has also been shown to induce the expression of the autophagy regulator *ATG16L1*, such that low vitamin D results in reduced ATG16L1 and reduced autophagy by Paneth cells in the intestines, leading to bacterial dysbiosis in the gut.[197] Prevention of autophagy maturation is also one of the mechanisms that HIV uses to prevent destruction by the infected cell, by its accessory protein Nef blocking beclin-1 function.[198] Due to its ability to induce *BECN1* and *ATG5 via* hCAP18, 1,25$(OH)_2D_3$ has also been shown *in vitro* to restrict HIV-1 replication in macrophages, by preventing autophagic blockage, promoting autophagosome–lysosome fusion.[199]

Another antimicrobial peptide human β-defensin 2 (HBD2, encoded by *DEFB4*) has also been shown to be induced by 1,25$(OH)_2D_3$ during *M. tuberculosis* infection.[200,201] In comparison with CAMP, the *DEFB4* promoter only has one VDRE, but two NF-κB binding sites. Consequently, its expression is regulated by dual signaling mechanisms, with vitamin D a smaller component.[202] RSV infection induces HBD2 *via* NF-κB signaling and HBD2 decreases RSV infectivity by blocking viral entry.[203] HBD2 binds directly to the HIV virion, preventing infection as well as having indirect effects on HIV infection through its down-regulation of the HIV co-receptor CXCR4 expression on the surface of CD4+ T cells *via* an increase in internalization.[204,205] Conversely, HBD2 is ineffectual against HSV and vaccinia virus,[188,206] while indirectly killing IAV through inducing aggregation of IAV particles to increase their uptake and respiratory burst by neutrophils.[207]

Recently, 1,25$(OH)_2D_3$ was also found to regulate microRNA expression, including inducing miRNA-22, which targets NFAT5, a regulator of HIV-1 LTR transcription in macrophages.[171,208] Thus there is the possibility that miRNA induction may be another mechanism by which vitamin D inhibits viral and bacterial replication.[209]

Anti-inflammatory effect of vitamin D

Paradoxically, despite its ability to induce NF-κB *via* NOD2 activation,[201] 1,25$(OH)_2D_3$ has profound anti-inflammatory effects

by inhibiting Mitogen-activated protein kinases (MAPK) and NF-κB signaling. The expression of MAPK phosphatase-1 (MKP-1, which dephosphorylates activated MAPK) is up-regulated in human MN by $1,25(OH)_2D$ and this is associated with increased binding of the nVDR and increased histone H4 acetylation at the VDRE in the MKP-1 promoter.[210] NF-κB activity is similarly inhibited by $1,25(OH)_2D_3$ by increasing IκBα levels and decreasing its phosphorylation (the first step in the degradation of the NF-κB inhibitor IκBα), leading to decreased NF-κB nuclear translocation and activity.[211] As such, vitamin D inhibits the NF-κB-induced type-1 pro-inflammatory cytokines IL-1β, IL-6, IL-8, IL-12p40, IL-23, IFNγ and TNF, and induces the anti-inflammatory cytokine IL-10 in MN, MDM and DC during bacterial and viral infections.[212–216] This suggests that vitamin D can reduce the severity of infection by decreasing the overall inflammatory state. Similarly, vitamin D has also been shown to inhibit IFNγ induced chemokines CXCL9 and CXLC10, which have been associated with reduced accumulation of pathogenic T cells in experimental cerebral malaria[55] and an improvement in the lymphocyte/monocyte ratio in TB.[217]

While vitamin D has the potential to decrease viral replication *via* autophagy induction, it also has the potential to reduce viral replication through the inhibition of NF-κB signaling, as cells with low NF-κB are resistant to viral infection, particularly influenza and HIV. As such it inhibits the reactivation of latent HIV infection in T cells *in vitro*.[218] Mortality in these infections is also correlated to the production of pro-inflammatory cytokines. Vitamin D may therefore protect against adverse outcomes of infection by inhibiting NF-κB and reducing the secretion of pro-inflammatory mediators.

We have recently shown that $25(OH)D_3$ also induces the expression of the natural innate inhibitor IL-37 in macrophages during *M. tuberculosis* infection.[213] IL-37, a member of the IL-1 family, has recently been identified to suppress macrophage TLR-induced cytokine and chemokine secretion, almost completely for IL-1α, TNF and IL-6 and somewhat for IL-1β, IL-12, G-CSF, and GM-CSF, independently of IL-10 and IL-1RA. IL-37 primarily mediates its effect by translocating to the nucleus and forming a complex with Smad3 as well as reducing the phosphorylation of p38 MAPK and STAT1-4. Secreted IL-37 also has extracellular effects, blocking IL-18R signaling and antagonizing IL-18 mediated-responses, which promote neutrophil chemotaxis.[219,220]

Vitamin D also promotes an anti-inflammatory response by inhibiting the maturation of DC, blocking CD14 down-regulation and inhibiting cell surface expression of MHC-class II molecules, CD40, CD80, CD83 and CD86.[214,215,221] Functionally, this results in the inhibition of chemokine secretion, a reduced capacity to activate Th1 T cell proliferation and production of Th1 and Th17 cytokines and induction of mature DC apoptosis. The DC switches to a tolerogenic phenotype, increasing production of Th2 cytokines and promotion of differentiation of naïve T cells into FoxP3 expressing Tregs.[222] Direct treatment of human CD8+ and CD4+ T cells with $1,25(OH)_2D$ also promotes a Th2 phenotype, reducing the number of IL-2 secreting T cells and completely blocking IFNγ, IL-17 and IL-21 production.[223,224]

The *in vitro* generation of Tregs by $1,25(OH)_2D$ has also been validated *in vivo* in studies showing that seasonal vitamin D deficiency is associated with decreased Foxp3 expression by Tregs and that serum 25(OH)D levels are correlated with Treg function.[58,224] We have also shown that $1,25(OH)_2D$ induces IL-10 from PBMC *in vitro*,[225] and vitamin D supplementation increases IL-4 secretion in whole blood *M. tuberculosis* antigen stimulation assays,[217] supporting the fact that vitamin D polarizes towards a Th2 response. Taken together, the studies above indicate that the immunomodulatory effects of $1,25(OH)_2D_3$ are dependent on the activity and environment of its target cells at the time of exposure. The relevance of these *in vitro* findings to the clinical situation may also be limited, and while there are some *in vivo* findings in animal models, more findings from clinical trials are needed to characterise the effect of vitamin D supplementation on human T cell responses, particularly during infection with different pathogens.

Vitamin D, cellular recruitment and tissue destruction

One of the hallmarks of infection is inflammation and tissue destruction, drivers of morbidity and mortality in disease. We have demonstrated that $1,25(OH)_2D$ inhibits the expression, secretion and activity of matrix metalloproteinaes (MMP), which are linked to tissue remodelling in TB and cerebral malaria due to their ability to degrade all components of the extracellular matrix (ECM).[225–227]

While the majority of studies on MMP focus on tissue destruction, MMP also plays a role in regulating inflammation. As endopeptidases they have been shown to release TNF and IL-6 from cell surfaces and inactivate IL-1β.[228] Thus again they have the ability to control viral replication by indirectly modulating cytokine production. Moreover, MMP regulates cell recruitment by processing chemokines and through cleaving fragments of ECM which act as chemotactic signals for inflammatory cells, including elastin degradation products in lung parenchyma.[229,230]

As mentioned previously, vitamin D-inducible cathelicidin and defensins also possess chemotactic activity. LL-37 induces CXCL8 secretion from epithelial cells[231] and has chemotactic activity for neutrophils, MN, and some T-cells,[232] while HBD2 exhibits chemotactic activity for MC[233] and some T-cells.[234,235] Vitamin D may therefore have multiple effects on resolving and preventing lung tissue destruction during infection as well as resolving pathology and restoring lung function during disease treatment, through regulating cell recruitment and tissue remodeling.

Vitamin D and vaccine efficacy

Due to the immunomodulatory properties of $1,25(OH)_2D$, vitamin D status has been investigated as an immune correlate of efficacy in multiple vaccine trials, with the suggestion that high vitamin D levels will inhibit vaccine efficacy. In two studies investigating the efficacy of influenza vaccine in HIV-

infected individuals, vitamin D deficiency did explain poorer vaccine outcome, and vitamin D supplementation did not improve outcome, as measured by seroconversion or seroprotection.[236,237] Similarly, vitamin D status was not associated with influenza seroconvesion in HIV uninfected children, adolescents or elderly individuals.[238,239]

Conversely, the TB vaccine BCG induces vitamin D deficiency up to 9 months following vaccination, potentially through increased *CYP27B1* expression by the live BCG vaccine. Moreover, there was a strong inverse correlation between 25(OH)D levels and IFNγ production to *M. tuberculosis* antigens and it was suggested that the modulation of vitamin D status by BCG may contribute to non-specific effects often observed with BCG vaccination.[240] As such, a study looking at the off-target effects of BCG showed that co-administration of $1,25(OH)_2D_3$ with BCG was able to enhance the effect of BCG on the cytotoxic ability of monocyte targeting cancer cells and prolonged the survival of mice, compared to those given BCG alone.[241]

Vitamin D supplementation trials

Cod liver oil. The first use of vitamin D as a therapeutic came quite by chance, due to its high content in cod liver oil, together with vitamin A, which was used to treat a range of infections in the pre-antibiotic era. An observational study from 1848 (non-placebo controlled) of cod liver oil given to TB patients in the UK concluded that "Cod liver oil possesses the property of controlling pulmonary consumption to a greater extent than any other agent hitherto tried".[242] Similar historic studies giving cod liver oil to children with measles showed no effect on reducing mortality, but it was found that children receiving the equivalent amount of vitamin D as that contained in cod liver oil had a reduced risk of developing pneumonia.[243] This observation has also been seen in more recent trials of vitamin D for treating TB, where reduced respiratory tract infection (RTI) was observed in those receiving high-dose vitamin D.[244] Cod liver oil given in conjunction with antimalarial drugs has also been shown to reduce the death rate in a mouse malaria model infected with *Plasmodium berghei*.[245]

Bacterial infection. Perhaps the disease that has had the greatest number of human trials to investigate the effect of vitamin D supplementation is TB. Supplementation of TB contacts with a single bolus dose of vitamin D_2 (100 000 IU) was shown, *ex vivo*, to enhance whole-blood restriction of *M. tuberculosis* growth.[246] Based on these results we were involved in a trial of high-dose adjunctive vitamin D_3 (100 000 IU, fortnightly for 8 weeks) during intensive phase treatment of pulmonary TB patients in London, UK. There was a trend towards a reduction in median time to sputum culture conversion in the intention to treat arm and a significant reduction in smear conversion in the per protocol cohort.[217,244] In subset analysis, we also identified a significant interaction between response to vitamin D_3 and a VDR polymorphism, suggesting that some people will have greater benefit from the supplementation than others. We found that fortnightly doses of 100 000 IU (approx. 7000 IU per day) only increased the mean 25(OH)D, in the entire cohort, above the optimal threshold of 75 nM L^{-1} after 4 weeks. We hypothesise that a greater antimicrobial effect of vitamin D_3 may be achieved with a higher, more frequent dose, or through supplementation with 25(OH)D_3 rather than vitamin D_3 to rapidly raise serum 25(OH)D levels.

A recent meta-analysis of 5 vitamin D trials in TB has shown a non-significant reduction in time to culture conversion following 6 weeks of vitamin D supplementation.[247] However, in all of these trials, there are interesting outcomes which are underpowered, including a reduced time to culture conversion in multi-drug-resistant (MDR)-TB cases, which suggests that vitamin D may be effective when first line drugs fail.[248] A study from India also showed that VDR polymorphisms are positively correlated with MDR-TB and that vitamin D status was lowest in MDR-TB patients and was inversely correlated to time to sputum smear conversion.[249] Furthermore, in most of these trials, HIV-infected individuals were excluded, but given the likely beneficial effect of HIV reservoir reduction, trials in this population are warranted.

Nonetheless, despite the inconclusive effect of vitamin D_3 on *M. tuberculosis* clearance, we did find a significantly greater and widespread reduction in inflammatory markers in those receiving vitamin D_3 during anti-TB therapy, compared to placebo, irrespective of VDR polymorphism.[217] Moreover, we found that vitamin D_3 supplementation increased the lymphocyte : monocyte ratio, previously shown to be a marker of healing lesions in a rabbit model of TB,[250] and accelerated the TB therapy-induced reduction in acute phase markers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and IFNγ, CXCL9 and CXCL10.[217] This suggests that vitamin D's greatest role may be resolution of pathologic inflammation during TB treatment.

While the anti-inflammatory effect of vitamin D may be useful during treatment, maintaining vitamin D sufficiency prior to infection could lead to ineffective inflammatory responses during initial infection. However, it is hypothesised that in those with latent TB or acute infection, vitamin D enhances anti-mycobacterial activity *via* AMP and autophagy induction and, at the same time, limits excessive inflammation associated with disease activation.[251]

Viral infection. A number of recent studies have also looked at vitamin D supplementation of children and adults with HIV, with varying results. The effect of supplementation depends on the antiretroviral (ARV) therapy regime the individual is on, likely due to the interaction between the ARV and vitamin D metabolism, with efavirenz and nevirapine associated with a positive increase in 25(OH)D levels, compared to protease inhibitor-based treatments.[252,253] The greatest effect of supplementation has been seen on changing the phenotype of circulating CD4-T cells, increasing the proportion of Tregs and naïve T-helper cells, and reducing the proportion of Th17 cells.[254,255] High-dose supplementation was also associated with decreased viral load and 25(OH)D levels were shown to predict viral load in a small subset analysis.[252,254] We have also shown that seasonal vitamin D deficiency is associated with

increased HIV-1 replication in PBMC, when infected *ex vivo*, and that this can be reversed in winter by 6 weeks of high-dose oral vitamin D supplementation.[60]

In chronic hepatitis C patients, response to interferon and ribavirn therapy is significantly associated with vitamin D status, with a higher baseline 25(OH)D predicting a sustained viral response (SVR), and vitamin D supplementation enhancing the response.[256,257] The effect of baseline vitamin D status and SVR was also shown to be further exacerbated according to the presence of a vitamin D binding protein polymorphism.[258] High dose vitamin D supplementation of patients with multiple sclerosis decreases antibodies against EBV, suggesting clearance of latent infection, but it had no effect on cytomegalovirus or varicella zoster virus.[259,260]

Finally, a recent meta-analysis of 11 studies showed that vitamin D supplementation can prevent RTI, most commonly caused by influenza-virus and *S. pneumonia*, with an odds ratio (OR) of 0.64.[261] This included studies of children and the elderly, those most at risk of RTI, and showed that frequent low doses were more effective than infrequent high doses, indicating the dose and frequency of the supplementation are extremely important for the utility of vitamin D for preventing infectious disease. A similar meta-analysis of 39 studies found overt heterogeneity in study design, that observational studies found a significant effect of vitamin D deficiency on lower RTI and that vitamin D supplementation studies had conflicting results, primarily related to differences in vitamin D dose, and baseline vitamin D status.[262]

Vitamin D-mediated and -independent effects of UVR

One of the topics that have emerged from the previous sections is that UVR exposure, although necessary (in respect of vitamin D production) and practically unavoidable, is not without potential mutagenic and immunosuppressive consequences. The effect of UVR on human infections has been recently associated with vitamin D production and subsequent regulation of immune function in a wide variety of cell types. But to what extent is the UVR effect on infectious diseases directly linked to vitamin D and to what extent are they independent, or even complementary?

UVR and vitamin D location of action

As shown in Fig. 1 the effect of UVR is primarily mediated through DNA damage and generation of PP, leading to production and subsequent activation of many mediators (including cytokines, AMPs and alarmins) and also homeostatic mechanisms leading to DNA repair, failure of which causes the activation of immunosuppressive mediators. The effect is local, limited to skin cells in most cases, such as keratinocytes, melanocytes, dDC and T cells. UVR can also have a limited systemic effect through the action of cytokines secreted into circulation.

Conversely, vitamin D is produced from 7-DHC in the skin and its metabolites can act locally or *via* their transport in the circulation to reach various body parts. Autocrine or paracrine production of $1,25(OH)_2D$ can lead to tissue specific activation of the VDR resulting in cellular functions key to a successful response to invading pathogens, including: an increased phagocytic capacity of macrophages, downstream production of AMP, ROS and NO, inhibition of MMP, production of regulatory cytokines and polarization of T cells towards a Th2 and Treg phenotype. From this it is clear that while UV mediated effects are mostly local and can become systemic through secreted cytokines, the effect of vitamin D is more far reaching and is mediated through a dedicated receptor on both the cell surface and in the nucleus of a variety of immune and tissue-specific cells.

Vitamin D-independent UVR immunomodulation

The only true way to dissect the vitamin D-mediated and -independent effects of UVR on susceptibility to infectious disease is by the use of randomised controlled trials of vitamin D supplementation and UVR exposure or the use of vitamin D pathway knock-out animal models. The presence of a VDRE in the promoter of CAMP being a unique adaptation in higher primates[182] also allows murine models to be used to study the AMP-independent immunomodulatory function of vitamin D during infection and the vitamin D-independent action of UVR-induced CRAMP (the murine homologue of CAMP).[263] The fact that UVR exposure induces AMP in mice indicates that UVR can induce AMP independently of UVR-induced vitamin D production.[101]

Due to the formation of vitamin D from UVR being inherently linked to the level of UVB, vitamin D-independent effects of UVR can also be mediated through the action of UVA. This wavelength of radiation, despite having DNA damaging effects and causing disruption of the skin pathogen barrier, also promotes ROS production, which impacts pathogen viability, and induces heme oxygenase 1 (HO-1), which has an antioxidant and immunoprotective function.

Finally, despite the overlapping effects of UVR and vitamin D on immunosuppression, there is evidence that UVR can mediate the effect in a vitamin D-independent fashion. This was demonstrated recently in the autoimmune encephalitis mice model where repeated UVR exposures lessened the severity of clinical symptoms without altering 25(OH)D levels.[264] In another study male vitamin D-deficient mice were unable to make 25(OH)D in response to UVR when vitamin D deficiency was induced by dietary restriction. These mice also showed systemic immunosuppression after erythemal UVR, showing that immunosuppression can be independent of the effect of vitamin D.[265]

UVR and vitamin D cumulative immunomodulation

A common theme that has emerged from both UVR and vitamin D studies is that both lead to immunosuppression *via* the adaptive immune system and are protective when they activate the innate immune system, especially *via* the induction of

AMP (Fig. 2). One factor to keep in mind is that UVR exposure induced immunomodulation and the production of vitamin D are not mutually exclusive events in the skin, but are rather two different outcomes of the UVR exposure. However, their effects also vary according to the exposure to and skin penetration of the different wavelengths of UVR and this is one way by which their independent effects can be disentangled. Infectious disease outcomes following UV exposure which also lead to changes in vitamin D levels would represent a scenario for cumulative effects.

Keratinocytes have the enzymatic machinery to make active vitamin D (Fig. 1). Both UV radiation and topical application a vitamin D analog change the number and function of Tregs in the dLN at the site of irradiation/application.[266] Knocking down VDR prevents these effects, suggesting that the effect of UVR on Treg migration is mediated by vitamin D. So, we can conclude that both UVR and UVR-mediated vitamin D production can work in conjunction to modulate the immune response.

Comparison of the effects of UVR and vitamin D on the outcomes of infectious disease

From the evidence presented in this review, we can identify four key factors for the outcome of infection: host fitness, pathogen fitness, and the prevailing environmental and social conditions. UVR radiation affects all of the above aspects. It is a driver of host fitness by virtue of its interaction with the skin, which can lead to various outcomes, depending on the UVR dose received. This dose is affected by the duration of exposure, the time of day and year of exposure, amount of skin exposed, degree of skin pigmentation and geographical location during exposure. As a local and sometimes systemic suppressor of immunity (Fig. 1) UVR can affect host fitness to a substantial degree, and in some cases can lead to reactivation of latent infection or an insufficient protective immune response to invading pathogens or administered vaccines. UVR also contributes to host immunity *via* its vital role in the synthesis of vitamin D.

Apart from these functions, UVR also modifies pathogen fitness by not only governing the skin microbiome but also the species diversity of the other pathogens prevalent in a given area. It does so by contributing to the direct killing of pathogens through heat generation and DNA-damage. Thus UVR and its product, vitamin D, have a major role in defining the prevalence and outcome of infectious disease.

In animal models, while UVR exposure leads to increased immunosuppression to pathogens such as *C. albicans*, *L. major*, *L. monocytogenes*, HSV and *M. bovis* BCG, vitamin D has been shown to have protective effects against *L. monocytogenes* and *M. bovis* BCG, no effect against *C. albicans* and HSV and a weakened response to *L. major*.[86] A small degree of concordance in the effect is seen in human association studies where both UVR and vitamin D increased the incedence of disease caused by HSV and reduced the incedence of disease caused by IAV and *M. tuberculosis*.[86]

While heliotherapy was useful historically for the treatment of non-pulmonary skin TB and surgical TB,[267] UVR has variable effects on *M. tuberculosis* due to its ability to repair DNA damage and results from placebo controlled trials have proven to be inconclusive for oral vitamin D treatment of TB.[74,247,262]

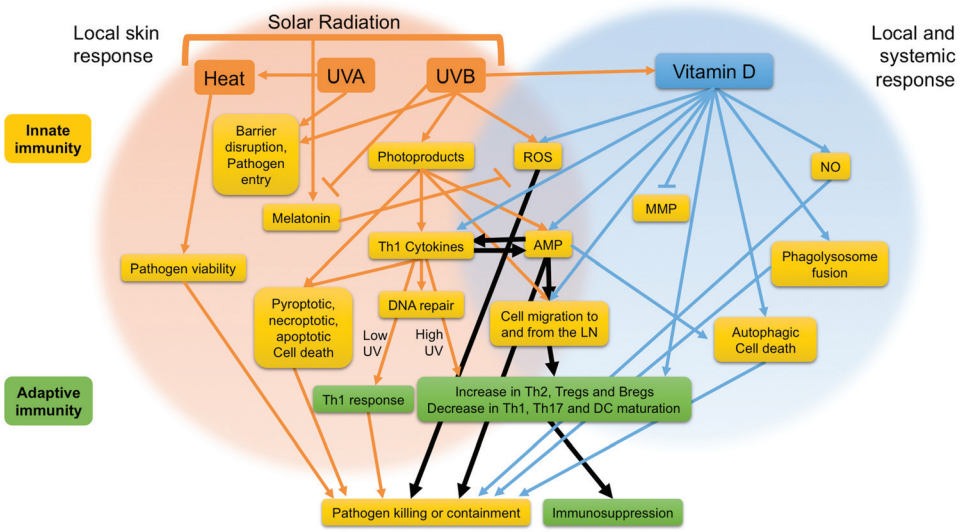

Fig. 2 The independent and overlapping effects of UVR and vitamin D on the cellular response to infection. Individual components of solar radiation, UVA, UVB and heat generation, are linked to their downstream immune function, inducing vitamin D production. While some effects are exclusive to UVR (orange lines) and some are exclusive to vitamin D (blue lines) there is a great degree of overlap between various components (black lines), particularly for antimicrobial peptide (AMP) induction and T helper (Th)2 and regulatory T cell (Treg) differentiation. The effect of UVR is primarily localised to the skin, while the vitamin D effects can occur in the skin and systemically in immune cells and in various tissue sites, culminating in pathogen killing and immnosuppression. Abbreviations: Bregs, regulatory B cells; DC, dendritic cells; MMP, matrix metalloproteinase; NO, nitric oxide; ROS, reactive oxygen species.

Vitamin D supplementation is protective for IAV[261] but the direct effect of UVR on IAV in humans has not been determined in a clinical trial,[86] and studies in mice indicate that UVR exposure enhances mortality following IAV infection.[120]

While UVR and temperature can affect the environmental reservoir of the pathogen, it has been argued that since bacteria, directly transmitted viruses, and fungi are "internal" to the host, they are less directly affected by environmental variability and hence UVR has much less effect on their transmission. These taxa may more readily spread over longer distances *via* their hosts, and this should minimize the impact of environmental conditions.[268]

For a comparison of the true differences between the effect of UVR and vitamin D, studies designed to look at the effect independently and concomitantly are needed. One such study called the sun exposure and vitamin D supplementation study is underway.[269] Its aim is to tease out the effect of UVR exposure and vitamin D supplementation in the management of vitamin D insufficiency and the consequence of each strategy on immune and cardio-metabolic function. Only through research incorporating such study designs can the dependent and independent effects of UVR and vitamin D be delineated.

Conclusions

The underlying paradigm of science is that association alone is insufficient to determine causality. This can be no truer than for seasonal variation in UVR, vitamin D and infectious disease prevalence. Due to the many seasonal covariates (melatonin, temperature, humidity, favourable transmission dynamics, social behaviour changes), there are many other factors which could lead to, and more likely compound, the seasonality of infectious disease prevalence that is associated with seasonal vitamin D deficiency at high latitudes. Nevertheless, it is clear that (1) UVR has both vitamin D-dependent and -independent effects on infectious diseases, (2) that these effects vary depending on the pathogen of interest and (3) that the effects can be cumulative, complementary or antagonistic.

It is therefore clear that future clinical trials need to be designed with the greatest chance of a meaningful outcome for each pathogen of interest. Results from one pathogen or one cell type, particularly if not a human cell, cannot be generalized to the outcome of all human infections. We need to determine the optimal threshold of vitamin D and UVR exposure for the mechanism of action for the disease process and for the particular population that is being targeted which may even require the need to define and understand the effect of population-specific genetic variants. Once the target level is identified, for the population of interest, the correct dose and dosing interval strategy needs to be chosen, with trials moving towards more frequent vitamin D dosing and away from enrolling vitamin D sufficient individuals. Alternative study designs to investigate the contribution of UV exposure to disease prevalence under the same climatic conditions (somewhat controlling for pathogen fitness) could include comparisons between urban and rural populations with the same genetic background, in the same relative geographical location, or individuals with varying skin pigmentation in the same location, as long as all other socio-economic and genetic factors are controlled for. Without better-designed studies, the unique properties of UVR and vitamin D that can be attained through 'safe' sun exposure or supplementation will remain underutilized in preventing infectious diseases.

Abbreviations

$1,25(OH)_2D$	1α,25-Dihydroxy-vitamin D
25(OH)D	25-Hydroxy-vitamin D
7-DHC	7-Dehydrocholesterol
AHR	Aryl hydrocarbon receptor
AMP	Antimicrobial peptide
APC	Antigen presenting cell
ARV	Antiretroviral
BCG	Bacillus Calmette-Guérin
CPD	Cyclobutane pyrimidine dimers
dDC	Dermal dendritic cell
dLN	Draining lymph node
DC	Dendritic cell
DTH	Delayed type hypersensitivity
EBV	Epstein-Barr virus
ECM	Extracellular matrix
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus type 1
IAV	Influenza A virus
IL	Interleukin
LC	Langerhans cells
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinases
MC	Mast Cell
MDM	Monocyte-derived macrophages
MN	Monocyte
mVDR	Membrane vitamin D receptor
NK	Natural Killer cells
NO	Nitric oxide
nVDR	Nuclear vitamin D receptor
PBMC	Peripheral blood mononuclear cells
PI3K	Phosphatidylinositol 3-kinase
PP	Photo products
PRR	Pattern recognition receptor
ROS	Reactive oxygen species
RSV	Respiratory syncytial virus (RSV)
RTI	Respiratory tract infections
RXR	Retinoid X receptor
TB	Tuberculosis
Th	T helper
TLR	Toll-like receptors
Treg	Regulatory T cells
UCA	*trans*-Urocanic acid
UVA	Ultraviolet A radiation

UVB	Ultraviolet B radiation
UVR	Ultraviolet radiation
VDRE	Vitamin D response elements

Acknowledgements

Abhimanyu thanks the National Research Foundation, South Africa (NRF Free-standing UID: 88297) and the Clinical Infectious Disease Research Initiative for his Postdoctoral Fellowship. A. K. Coussens is supported by the Medical Research Council of South Africa (SHIP-02-2013), the Academy of Science of South Africa (Sydney Brenner Fellowship) and the National Institute of Health TB Research Unit (TBRU-BURU).

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