Chapter 14

Public Health, Infection and Infectious Agents: The Etiology is Seemingly Always 'Clever'

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1. Introduction

While humans have been struggling to search for the best means to control infection to humans, infectious agents have been evolving with new means for evading efforts by the body immune defense to arrest infections. We know that infectious agents escape body defense mechanisms through evasion of the immune system or development of resistance to drugs intended to inhibit growth or activity of these organisms. Sometimes using host's resources to flourish and unfairly destroying the host and its resources! Malaria parasite for example, infects human red blood cells, produce clones of itself with different levels of resistance and immune evasion diversity. The virus e.g. retroviruses, use human genetic materials to reproduce their own nucleic acids (reverse transcription) within infected cells, altering planned activities, consequently damaging the host cells! This chapter explores step by step why we can regard infecting organisms as clever than us.

2. Viral infections

Host immune evasion

Existing belief indicates that from primordial soup in which life originated [1], viruses developed together with variety of their hosts. In these past millions of years, the hosts have developed a complex immune defense system against viral infections but the intelligent viruses have though developed strategies to evade these host defences and replicate themselves using host's resources. The host immune response is responsible for defence against viruses and their consequences. It consists of a complex interwoven series of chemical, cytokine and cellular interactions that work in synergy in an attempt to remove these invading

viruses from the body. The outcome of viral infections in an animal is determined by a balance between the speed of viral replication and spread, as well as the immune response [2]. Yet, viruses are regarded as important natural means of transferring genes between different species, which increases genetic diversity while in seat to drive evolution [3].

The concern for infections and their evasion strategies arises from the fact that vast of infections and all poverty related infections are predominantly found in Africa, for example HIV/AIDS (Figure 1).

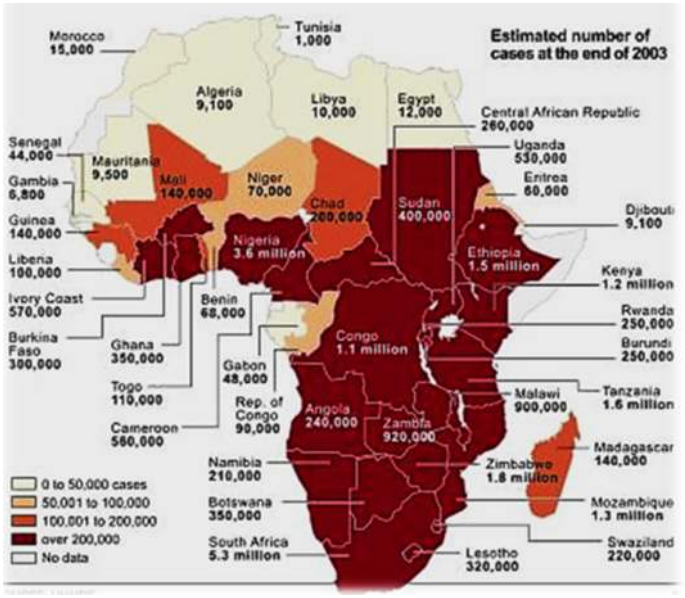

Figure 1. More than two-third of the estimated 39.4 million people living with HIV worldwide are found in Africa. (*Source: UNSAIDS*)

The host immunity consists of innate and adaptive immune responses geared at restraining the viral and other pathogen invasion to keep the host healthy. The innate immune responses comprise of effector cells that include macrophages, neutrophils, natural killer (NK) cells, mast cells, basophils and eosinophils. The humoral component of the innate immune response includes the complement cascade, interferon and a host of cytokines and chemokines associated with inflammation. These cytokines and chemokines interact to attract, activate and control the function of effector cells. NK cells are prime effector cells of the innate immune response to virally infected cells and they act by destroying infected cells through release of effector granules such as perforins and granzymes. Detection of virally infected cells and control of activation is achieved through the balance of activating and inhibitory receptors on the NK cells. All nucleated cells within the body express Major Histocompatibility Complex (MHC)-1 molecule on their surface. MHC-1 molecules bind to receptors (CD94/

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NKG2A) on the surface of NK cells and act as inhibitors of NK cell activity. If these MHC-1 molecules are not present or reduced in number on a cell (such as virally infected cell), there is no inhibition of NK cell and the NK cell destroy the infected cell. To counter effect this action by NK cells, the virus cleverly evade this immune protective response through various ways namely: modification of expression of ligands on the surface of the infected cell either increased expression of inhibitory ligands, expression of viral mimics of inhibitory ligands or decreased expression of activating ligands, inhibition of cytokines such as Interferon-γ (IFN-γ) or IL-18, viral molecules that competitively bind IL-18 receptors or disruption of the release of effector molecules like perforins and granzymes. These potentially cleverly strategies enable viruses to escape punishment from host defence, including the complement system, antibodies, interferon, T-cells, cytokines, and programmed cell death, apoptosis [4,5]. Humans have been doing various researches in attempt to block these evasive mechanisms by the virus but the virus always plans different means as though fighting against invading viruses remains to be a vicious cycle.

The remarkable number and the complexities of the virus adaptations to suit the diverse immune response approach by the host poses a challenge to human intelligence on fighting infectious agents. It is said that through virus-host interactions at molecular level, interference occurs through gene regulation that consequently modulates a range of fundamental cellular processes [6]. While it is not surprising that the viruses develop strategies to overcome host defences, the great rapidity with which viruses adapt and replicate within host cells to survive the complex immune mechanisms with multiple adaptations has given the virus an evolutional complement. The virus genome is relatively small as compared to most of its hosts and many viruses produce proteins that act in multiple different ways on different portions of the immune system. This creates a challenge for which best approach should scientists use to counter effect these virus strategical intelligence.

Antiviral Resistance

Anti-viral resistance is an additional issue of concern. Like with other infections, drug resistance to anti-vials and clinical implication has been described [7]. Nevertheless, the management of this drug resistance is suggested to be through optimization of host factors and drug delivery, selection of alternative therapies based on knowledge of mechanisms of resistance, and the development of new antivirals. All these are subject to intelligence by the virus to counter effect, which may be rapid as well! For example, prolonged drug exposure is said to lead to the selection of resistant strains which normally develop via viral mutations necessitating a strategical approach to restraint viral infections [8] which may include testing for resistance to drugs before therapy begins [9]. Proposed ways for possible blockade of immune evasion domains on viruses has been suggested including the suitability of the therapeutic and vaccine efficacy potential [10] but the constantly dynamic and regularly changing strategies for evasion by pathogenic viruses remain a critical challenge. Prescriptions ranging from single to multiple 'cocktail' drugs have been currently been given to people with HIV in an attempt to make emergence of resistance less likely. In such situation, the idea is such that even if a strain evolves resistance to one of the drugs, it will still succumb to other drugs in the combination. However, the virus has been able to evolve resistance to

more than one drug, some strains being resistant to all major classes of drugs used to combat the virus [11]. The virus which can develop resistant to reverse transcriptase (RT) inhibitors, protease inhibitors, fusion/entry inhibitors, integrase inhibitors as well as multidrug combinations fielding more than one class into a single product must be far clever than us! With the frequency of cross-resistance between drugs within a class said to be high, it further efforts to control viral replication more complicated [12-15]. This is because to combat virus strains from becoming resistant to specific antiretroviral drugs, healthcare providers have been recommending people infected with HIV to take a combination of highly active antiretroviral drugs therapy (HAART) to enable viruses resistant to single class of drugs not to have an escape route. In addition, some antiretroviral drugs have been combined into one pill, known as a 'fixed dose combination' to reduce the number of pills to be taken each day by the patient. Development of resistance to at least major classes of anti-retroviral drugs is a blow to the HAART strategy of combining drugs from at least two different antiretroviral drug classes for the purpose.

The major control in pathogen control is clearing of susceptible strains while maintaining spread of resistant strains. This is because once there is transmission of drug-resistant strains [16-18], it becomes difficult to contain the pathogen. Mutations in drug target markers is primarily important in development of drug resistance as indicated by Clavel and Hance [19] and genotyping for drug resistance markers by sequencing is a complex technology which presents a challenge for analysis, interpretation, and reporting [20]. This addresses the felt difficulties in containing infectious agents like viruses which are very minute with great survival strategies. The situation could be of substantial impact in sub-Saharan Africa where recent report on antiretroviral drugs indicates significant increase in prevalence resistance over time with possibility of spread of high levels of HIV-1 drug resistance in these resource-limited settings [21]. The findings also caution on possibility of the condition to potentially compromise the effectiveness of HIV treatment programs. An example of drugs and mechanisms of action and development of resistance is revealed in Table 1 with special attention on HIV virus.

Drugs	Mechanisms of Action	Mechanisms of Resistance
Nucleoside analogues Zidovudine Stavudine Lamivudine Didanosine Zalcitabine Abacavir	Analogues of normal nucleosides Active as triphosphate derivatives Incorporated into nascent viral DNA Prematurely terminate HIV DNA synthesis	Thymidine analogue mutations promote ATP-mediated and pyrophosphate-mediated excision of the incorporated terminator M184V or Q151M complex mutations impair incorporation of nucleoside analogues
Nucleotide analogues Tenofovir	Same as nucleoside analogues	K65R impairs incorporation of tenofovir into DNA

Drugs	Mechanisms of Action	Mechanisms of Resistance
		Thymidine analogue mutations often associated with cross-resistance to tenofovir
Nonnucleoside reverse-transcriptase inhibitors Nevirapine Efavirenz Delavirdine	Bind a hydrophobic pocket of HIV type 1 reverse transcriptase Block polymerization of viral DNA Inactive against HIV type 2	Mutations reduce affinity of the inhibitors for the enzyme Single mutations generally sufficient to induce high level of resistance
Protease inhibitors Saquinavir Ritonavir Indinavir Nelfinavir Amprenavir Lopinavir	Structure derived from natural peptidic substrates of the HIV type 1 protease Bind the active site of the protease	Mutations reduce affinity of the inhibitors for the enzyme High-level resistance requires accumulation of mutations
Fusion inhibitors Enfuvirtide	36-Amino-acid peptide derived from the HR2 domain of glycoprotein 41 Interferes with glycoprotein 41–dependent membrane fusion	Mutations affect HR1, a domain of glycoprotein 41 whose interaction with HR2 promotes membrane fusion

Table 1. Antiretroviral Agents Used in the Treatment of HIV InfectionSource: Clavel F, Hance [19].

3. Bacterial infections

Antigenic variation

One of the important characteristics of the host immune response is antigen-specificity through antibody production. In this context, once the host immune system is exposed to a certain pathogen, it develops a response that is memorable against that pathogen. Similar pathogen with similar proteins (immunologically called antigens) will be recognized as soon as the host encounters same infection. This ability by the host's immune response to remember previously encountered pathogen and act accordingly is termed immunological memory. This intelligence by the host's immune response is however not a big problem to bacterial pathogens. The surveillance by the immune response against invading infectious agents can still be escaped by the clever pathogen like bacteria. One way in which an infectious agent, particularly extracellular pathogens can evade immune surveillance is by altering its antigens against which the principal defence is the production of antibodies against their surface structures. This is called antigenic variation. Antigenic variation can be achieved through, existence in a wide variety of antigenic types by many infectious agents. Other means include antigenic drift (point mutations in the genes encoding for certain antigenic proteins) and programmed rearrangements in the DNA of some pathogens. For example

ability of the enteropathogenic Yersinia enterocolitica to survive and proliferate in host tissue is said to be favoured by suppression of cytokine response that significantly contributes to the evasion of antibacterial host defence against the pathogen [22]. We know that the immune system is highly diverse to counter effect the threats by various antigens from various pathogens but it seems that when we come to evolution, the pathogens evolve faster than the hosts! But why and how these pathogens look like they think ahead of higher organisms (their hosts)? It could mean that as the organism becomes complex the rate of evolution is slow as compared to lower organisms. It is known that the rate of evolutional change is governed by the life span of the species where, short-lived species are capable of changing faster compared to those with a longer life span [23]. On the other side of the coin floods of antigens per episode may probably confuse the stringent host's immune response. Bacterial pathogens for example, are said to dump more than 200 proteins into human macrophage cells, the 'effector proteins' [24]. In addition, these proteins are so similar to the human proteins enabling them to freely interfere with the body's immune response while protecting the pathogen. Despite the fact that even short-lived species such as bacteria, which have generation times measured in minutes, do not manifest noticeable evolutionary changes in a humans lifetime, in some cases, evolution rates can depend on mutation rates [23]. The changes that will definitely influence the survival strategy of the pathogen like bacteria in presence of host like humans and animals.

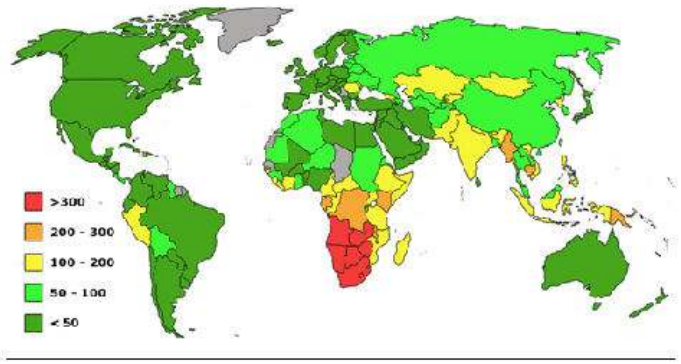

Figure 2. Global distribution of tuberculosis. In sub-Saharan Africa, TB remains the number one cause of death in HIV/Aids patients, and those infected with HIV show a much greater incidence of TB than those who are HIV-negative. WHO statistics do show, however, that HIV-positive adults receiving ARV treatment have substantially lower rates of TB infection than those who are not receiving treatment. This may not be the case following development of antiretroviral drug resistance!Source: http://myfundi.co.za/e/Global_distribution_of_diseases:_TB,_HIV/Aids,_cholera_and_malaria

Drug Resistance

Mimicry allows deadly bacteria to evade host's defense through continued sprouting of antibiotic resistance by simulating human proteins [24]. This process of "molecular mimicry" has led human bacterial pathogens which were at one time easily treatable with antibiotics to

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recently re-emerge as highly infectious public health threats. This situation has drawn attention for increased preparedness for emerging and re-emerging diseases [25]. In this context, the suggested 'fit-for purpose' approaches such as the inter-discipline merging with a focus on 'one health' approach, use of participatory epidemiology and disease surveillance and mobile technologies may offer opportunity for optimal use of limited resources to improve early detection, diagnosis and response to disease events which could eventually reduce the impact of such diseases to animal and human populations.

Antibiotic resistance bears serious importance in public health. In both humans and animals, drug resistant bacteria have been a threat to health and economy due to costs incurred in an attempt to contain the disease situation which may finally not work out. This resistance may be natural or develop after antibiotic use. In bacteria, induction of changes in ability to become antibiotic resistant is influenced by mutations which could be evolutional. This is despite mutations seemingly not having major effects on limiting evolution as diversity in morphological evolution (evolution of physical characteristics) has been found not to correlate well with DNA mutation rates [23]. With mutations, bacteria which were once susceptible to certain antibiotics are currently no longer controlled or killed by those antibiotics, the bacteria being able to survive and even multiply in the presence of a respective antibiotic agent. We have observed this in chronic diseases such as tuberculosis, bovine mastitis and many other bacterial diseases. Genome sequencing has indicated a known family of kinases circulating in modern drug resistant pathogens reflecting the prevalence of resistance even in microbiomes isolated from human use of antibiotics [26]. Bacterial resistance to formally useful drugs occur in such ways as preventing the antibiotic from getting to its target through changing the cell permeability for the drug or use ATP to pump drugs outside the cell, thus reducing the chances that the drug will kill the bacteria. Other means incudes changing the structure of the target for the drug such that the antibiotic can no longer recognize or bind to it. In addition, bacteria may destroy the drug through production of say, beta-lactamases that directly neutralize penicillin. Acquisition of resistance by bacteria may be achieved through transformation, transposon and scavenging of DNA remnants from other degraded bacteria. These all are intelligence by the pathogen that needs no higher organisms (hosts like human and animals) assistance but own capabilities. One would wonder where these sorts of intelligence come from.

4. Parasitic infections

An example of well-studied tropical infectious parasite is the malaria parasite, Plasmodium falciparum. A lot of challenges have been posed to scientific community as regards immune evasion by the malaria parasite due to its ability to overwhelm the impact of host's immune response and through resistance to drugs of choice for the disease. Various researches in immunology have in principle shown parasite evasion of host immunity to be ubiquitous involving a wide range of molecular mechanisms [27]. Immune evasion generates a large spectrum of pathogenic effects, such as cytokine blows and inflammation. The relationships between the benefits of immune evasion and its pathogenic consequences could reflect evo-

lutional and ecological host–parasite interactions. Such interactions have impacts on the dose, parasite virulence, immune defence strategies, immunopathology and host specificity [27]. Protective immunity to malaria for example is won by the parasite through its strategies used to evade host immunity, including antigen diversity/polymorphisms, antigen variation and total immune suppression [28].

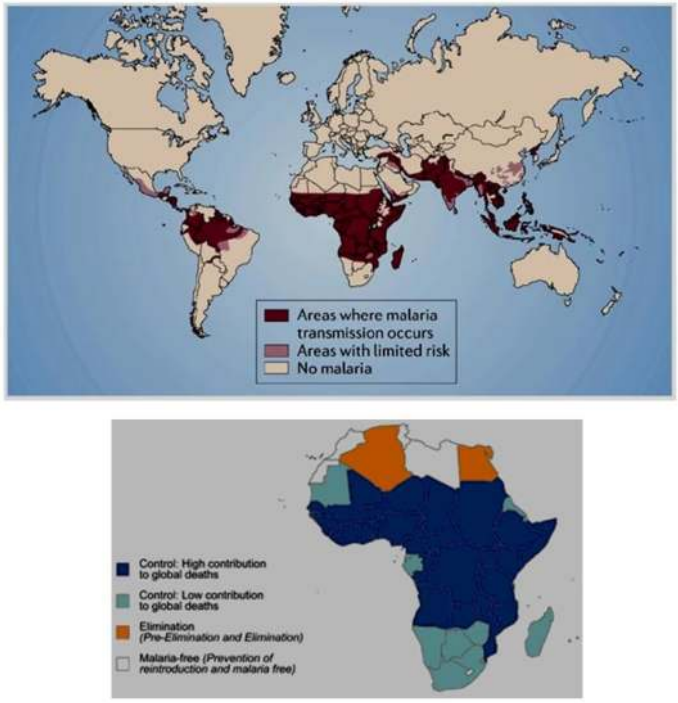

Figure 3. a:distribution of parasitic diseases, an example of malaria. See (figure above) the concentration of the disease insub-Saharan Africa. Source: http://www.nature.com/nrmicro/journal/v4/n9_supp/fig_tab/nrmicro1525_F2.html b:Despite the global distribution of malaria, high deaths are concentrated in Africa, south of Sahara where it also contributes to high deaths. This parasitic disease, despite antigen diversity, it is also resistant to most antimalarial drugs designed to restrain the disease. Consequently, the disease cause global economic and social burdens [29] particularly predominating in African countries. Source: http://www.nature.com/nrmicro/journal/v4/n9_supp/fig_tab/nrmicro1525_F2.html

Evidence from population genomics of the immune evasion (var) genes of Plasmodium falciparum [30] suggests recombination to play a key role in maintaining the extraordinary levels of polymorphism found in the immune evasion genes. Most malaria vaccine-candidate antigens have highly polymorphic surface proteins that elicit variant-specific immunity [31]. Nevertheless, this antigenic diversity is still beaten by an evasive malaria parasite as though no vaccine yet to arrest malaria troubles in endemic areas. Exploration on evolutional relationships for the design of vaccines based on ancestral sequences, with the potential for inducing

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cross-protection against a wide range of antigenic variants [32] has been proposed, but the parasite always seems to be ahead of the scientific community. Thus, despite efforts for understanding the mechanisms and patterns of genetic recombination and sequence variation designing vaccines that represent the worldwide repertoire of polymorphic malarial surface antigens may be difficult due to dynamic continuum of antigenic variation in the parasite.

Drug resistance is another way apart from immune evasion that the parasite uses to win the battle against host efforts to fight parasitic infections. A range of drugs for example has been used for malaria treatment over decades but have ended disapprovingly through development of drug resistance. Similar strategies have been used by other parasites in animals as well as in humans. Drug resistance and genetic studies on P. falciparum have revealed a limited geographical genetic diversity in a genetically homogeneous parasite population [33]. Studies on competitive facilitation of drug-resistant Plasmodium falciparum malaria have indicated the most highly resistant parasites to out-compete less fit parasite populations [34]. Consequently, these resistant strains overgrow under drug pressure posing a great threat that at one moment there might be an existence of a parasite population which is highly resistant to drug use. Systematic mapping of genetic variation in Plasmodium falciparum to locate other loci that can facilitate parasite drug resistance [35] is important. However, all these efforts will be of value to the scientific community if we will finally be able to contain the parasite than it being always a hero.

5. Fungal infections

Under the kingdom of Fungi are many species with a wide spectrum of diseases that can infect humans and other animals most of which being accidentally originating from exogenous sources by inhalation (e.g. Aspergillus spp., Cryptococcus neoformans or endemic mycoses) but also as commensals of the gastrointestinal tract (e.g. Candida spp.) or reactivation of a latent infection [36]. Clinical manifestation and severity of fungal infections, including transition from potentially commensals to infections depends on the patient's immune response, the host-pathogen interaction and ability of the infecting pathogenic fungus to evade the host immune response [37-40]. Like other infections, the immunity to fungal infections comprises of both innate and adaptive responses. These host defence mechanisms require induction and activation after infection through invariant molecular structures shared by large groups of pathogens (collectively called pathogen-associated molecular patterns, PAMPs) which are recognized by a set of pattern recognition receptors (PRRs) in the host immune defence cells, including Toll-like receptors (TLRs) [41]. However, intelligent is the host's defence, the fungus can defend better! Thus the fungus has developed a variety of evasive mechanisms to escape host defence while nourishing themselves within host's resources.

Immune evasion in fungal infections is not uncommon phenomenon. A pathogen with a variety of strategies enabling its effective survival within the host while able to evade immune detection to overcome the smart host immune response is said to be successful. The well-known strategies employed by fungal pathogens to evade host defense mechanisms includes shielding of stimu-

latory PAMPs, modulation of inflammatory signals, shedding of distraction components, persistence in intracellular environments and complement evasion [42]. Among evasion mechanisms to overcome both innate and adaptive immunity by some fungal infections is phase transition through expression of yeast-phase specific genes and alteration of cell wall components [43]. In Candida albicans infection, specific enzyme is secreted to degrade and deactivate a host antimicrobial peptide involved in the protection of the oral mucosa against the fungus thus enhancing its transition from commensal to pathogen [44].

Similar to other infections, fungal immune evasion when coupled with resistance to potential antifungal drugs poses a setback towards arresting diseases; their clinical and pathological consequences. Further, we have to admit diagnosis, epidemiology and mechanisms of antifungal drug resistance [45] to be a challenge in control of fungal infections. A recent study [46] for instance, has revealed geographic variations in fungal species and antifungal resistance rates distribution among isolates pointing out a focused surveillance on emerging resistance patterns in Candida infection (see Table 2). The study does not cover African continent but should be taken as a warning alarm for the potential risks developing countries like those in Africa may similarly be facing. Antifungal resistance has also been surveyed in Aspergillus species using molecular tools showing resistance potential for multiple antifungal drugs [47]. In the same study, new species were in addition, identified which could reflect emergence of new fungal species potentially resistant to drugs. Importantly, it is a reflection that screening using advanced tools may help to restrain disease transmission through procedures such as transplantation and blood transfusion. Surveillance networks that incorporate sequence-based identification of clinical isolates to determine the species distribution, the clinical disease and outcome of patients with invasive fungal species have been suggested [48]. Factors driving fungal composition are primarily global and indoor fungal composition is again said to be geographically patterned with more diversity observed in temperate zones than in the tropics [49]. But the proposition should be viewed with special precaution not to rule out the situation to similarly occur in the tropics. This is particularly critical as fungi are ubiquitous components of indoor human environments, with most contact between humans and microbes probable thus raising the possibility of contribution to spread of resistant strains during disease transmission. The idea is that application of antifungal drugs will definitely kill susceptible strains leaving resistant strains to prevail and circulate in the community of hosts they infect.

Available reports indicate a change in epidemiology of systemic fungal infections citing the key elements in selection of appropriate antifungal agent which include; the type of patient (solid-organ or stem-cell transplant), severity of immunosuppression, history of prolonged exposure to antifungal drugs, and knowledge of the genera and species of the infecting pathogen and its typical susceptibility pattern [50]. Canonn et al. [51] pointed out on efflux-mediated antifungal drug resistance with a list of antifungal drugs, their targets and possible resistance mechanisms. The authors finally, suggest among other approaches that scientists can deploy to identify and possibly design multifunctional drugs that inhibit conventional targets as well as the transcription factors responsible for the overexpression of efflux pumps and the pumps themselves. This idea was also previously addressed by Monk

and Goffeau [52]. But we should bear in mind that despite these all efforts, the microbes, having no laboratories for designing and formulating mechanisms for survival in the host, can still generate resistance markers through genetic mutations and other gene rearrangements. Concerns regarding the development of resistance to even the available few antifungal drugs have been raised [53] and new diagnostic tools for rapid, sensitive, and specific detection of fungi in clinical material has been proposed to be a mandatory for effective discovery and designing of appropriate drugs [54]. But how fast and quick are we ahead of the 'microbe thinking'? I always think that, if it was learning, then the microbes have been learning faster than human beings! Who amongst us can agree this view? It is through surveillance on infections, immunity, chemotherapeutics, evolutional characteristics and differences between lower and higher organisms that we can get answers.

Species	% of isolates by species and geographic region (n[b])				
	Asia-Pacific (51)	Latin America (348)	Europe (750)	North America (936)	Total (2,085)
C. albicans	56.9	43.6	55.2	43.4	48.41
C. glabrata	13.7	5.2	15.7	23.5	18.0
C. parapsilosis	13.7	25.6	13.7	17.1	17.2
C. tropicalis	11.7	17.0	7.3	10.5	10.5
C. krusei	2.0	1.4	2.5	1.6	1.9
C. lusitaniae	0.0	0.9	1.2	2.2	1.6
C. dubliniensis	0.0	0.3	0.8	1.0	0.8
C. guilliermondii	0.0	1.7	0.1	0.1	0.4
Misc.[a]	2.0	1.6	1.7	0.6	1.2

Table 2. Species distribution of Candida bloodstream infection isolates across geographic regions out of African continentsSpecies distribution of Candida bloodstream infection isolates across geographic regions: SENTRY Surveillance Program, 2008 to 2009. [a]Miscellaneous species including 6 isolates of C. kefyr, 2 each of C. rugosa, C. sake, and C. pelliculosa, 3 each of C. famata and C. lipolytica, and 1 each of C. lambica, C. utilis, C. haemulonii, C. norvegensis, and C. inconspicua.n[b]: number tested.Source: Pfaller et al. [46].

6. Summary

This chapter has discussed in brief, the human infectious agents, host immune response, immune evasion and drug resistance to various anti-pathogen drugs. The chapter highlighted how smart is the host's immune defence mechanisms against infectious agents and how the pathogens device mechanisms for escape and survival within host's territory. The net balance between host defence and pathogen defence evasion is the one which determines the fate of infection to either resolve or develop to clinical disease plus its pathological consequences. In most cases it seems the pathogen wins the battle due to its always far ahead

'thinking' for counter strategies. It remains a question as to whether the pathogens are clever than their hosts, including humans or is just a miss by human efforts to capture relevant pathogenic factors without which the infecting organisms would be harmless. The scientific community is highly acknowledged for the efforts and a synergistic multi-disciplinary approach to control striking infections, particularly those with cross-transmission to animals other than human beings (zoonotic infections). The concern is that with time, the selected resistant or immune evasive strains will remain in circulation within human and animal population making control extremely difficult. Consequently, it raises a worry that probably higher organisms have fewer chances for successful life in presence of lower organisms. Several efforts in research including experimental, clinical and immunological potential impact of improved nutrition to specific infections have been in place [54-69]. Despite these efforts, however, vaccine and drug developments have been made difficult by the tricky survival strategies by pathogens making improvement in health focusing in nutrition not as good as might be if the pathogens were not that clever. The remaining challenge is how to bring together willing interested partners (stakeholders) for joint efforts in control of diseases. Attention should also be directed to zoonotic infections such as tuberculosis whose resistance may develop in one species and be detrimental to other species for instance drug resistant Mycobacterium bovis from cattle infecting humans. The 'one health' concept in such circumstances will stand a greater chance of playing a role in limiting transmission of the diseases across species.

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References

[1] Strauss, E. G., Strauss, J. H., & Levine, A. J. (1996). Virus evolution. *Fields BN, Knipe DM, and Howley PM. (ed.) Fundamental virology, 3rd ed. New York: Raven Press*, 141-159.

[2] Diamond, M. S. (2003). Evasion of innate and adaptive immunity by flaviviruses. *Immunology and Cell Biology*, 81, 196-206.

[3] Canchaya, C., Fournous, G., Chibani-Chennoufi, S., Dillmann, M. L., & Brüssow, H. (2003). Phage as agents of lateral gene transfer. *Current. Opinion in Microbiology*, 6(4), 417-24.

[4] Alcami, A., & Koszinowski, U. H. (2000). Viral mechanisms of immune evasion. *Immunology Today*, 21, 447-455.

[5] Tortorella, D., Gewurz, B. E., Furman, M. H., Schust, D. J., & Ploegh, H. L. (2000). Viral subversion of the immune system. *Annual Review of Immunology*, 18, 861-926.

[6] Skalsky, R. L., & Cullen, B. R. (2010). Viruses, microRNAs, and Host Interactions. *Annual Review of Microbiology*, 64(1), 123-141.

[7] Strasfeld, L., & Chou, S. (2010). Antiviral Drug Resistance: Mechanisms and Clinical Implications. *Infectious Disease Clinics of North America*, 24(2), 413-437.

[8] Gammon, D. B., Snoeck, R., Fiten, P., Krecmerova, M., Holy, A., De Clercq, E., Opdenakker, G., Evans, D. H., & Andrei, G. (2008). Mechanism of Antiviral Drug Resistance of Vaccinia Virus: Identification of Residues in the Viral DNA Polymerase Conferring Differential Resistance to Antipoxvirus Drugs. *Journal of Virology*, 82(24), 12520-12534.

[9] Little, S. J., Holte, S., Routy-P, J., Daar, E. S., Markowitz, M., Collier, A. C., Koup, R. A., Mellors, J. W., Connick, E., Conway, B., Kilby, M., Wang, L., Whitcomb, J. M., Hellmann, N. S., & Richman, D. D. (2002). Antiretroviral-Drug Resistance among Patients Recently Infected with HIV. *New England Journal of Medicine*, 347(6), 385-394.

[10] Judson, K. A., Lubinski, J. M., Jiang, M., Chang, Y., Eisenberg, R. J., Cohen, G. H., & Friedman, H. M. (2003). Blocking Immune Evasion as a Novel Approach for Prevention and Treatment of Herpes Simplex Virus Infection. *Journal of Virology*, 77(23), 12639-12645.

[11] Shafer, R. W., Winters, MA, Palmer, S., & Merigan, T. C. (1998). Multiple concurrent reverse transcriptase and protease mutations and multidrug resistance of HIV-1 isolates from heavily treated patients. *Annals of Internal Medicine*, 128, 906-911.

[12] Hertogs, K., Bloor, S., Kemp, S. D., Van den, Eynde. C., Alcorn, T. M., Pauwels, R., Van Houtte, M., Staszewski, S., Miller, V., & Larder, AA. (2000). Phenotypic and genotypic analysis of clinical HIV-1 isolates reveals extensive protease inhibitor cross-resistance: a survey of over 6000 samples. *AIDS*, 14, 1203-1210.

[13] Richman, D. D. (1990). Susceptibility to nucleoside analogues of zidovudine-resistant isolates of human immunodeficiency virus. *American Journal of Medicine*, 88, 8S-10S.

[14] Miller, V., & Larder, BA. (2001). Mutational patterns in the HIV genome and cross-resistance following nucleoside and nucleotide analogue drug exposure. *Antiviral therapy*, 6(3), 25-44.

[15] Race, E., Dam, E., Obry, V., Paulous, S., & Clavel, F. (1999). Analysis of HIV cross-resistance to protease inhibitors using a rapid single-cycle recombinant virus assay for patients failing on combination therapies. *AIDS*, 13, 2061-8.

[16] Yerly, S., Kaiser, L., Race, E., Bru, J. P., Clavel, F., & Perrin, L. (1999). Transmission of antiretroviraldrug-resistant HIV-1 variants. *Lancet*, 354, 729-733.

[17] Little, S. J., Holte, S., Routy-P, J., Daar, E. S., Markowitz, M., Collier, A. C., Koup, R. A., Mellors, J. W., Connick, E., Conway, B., Kilby, M., Wang, L., Whitcomb, J. M., Hellmann, N. S., & Richman, D. D. (2002). Antiretroviral-drug resistance among patients recently infected with HIV. *New England Journal of Medicine*, 347(6), 385-394.

[18] Grant, R. M., Hecht, F. M., Warmerdam, M., Liu, L., Liegler, T., Petropoulos, C. J., Hellmann, N. S., Chesney, M., Busch, M. P., & Kahn, J. O. (2002). Time trends in primary HIV-1 drug resistance among recently infected persons. *The Journal of the American Medical Association*, 288, 181-188.

[19] Clavel, F., & Hance, A. J. (2004). HIV Drug Resistance. *New England Journal of Medicine*, 350, 1023-1035.

[20] Erali, E., Page, S., Reimer, L. G., & Hillyard, D. R. (2001). Human Immunodeficiency Virus Type 1 Drug Resistance Testing: a Comparison of Three Sequence-Based Methods. *Journal of Clinical Microbiology*, 39(6), 2157-2165.

[21] Gupta, R. K., Jordan, M. R., Sultan, B. J., Hill, A., Davis, D. H. J., Gregson, J., Sawyer, A. W., Hamers, R. L., Ndembi, N., Pillay, D., & Bertagnolio, S. (2012). Global trends in antiretroviral resistance in treatment-naive individuals with HIV after rollout of antiretroviral treatment in resource-limited settings: a global collaborative study and meta-regression analysis. *The Lancet*, 10.1016/S0140-6736(12)61038-1.

[22] Beuscher, H. U., Rödel, F., Forsberg, A., & Röllinghoff, M. (1995). Bacterial evasion of host immune defense: Yersinia enterocolitica encodes a suppressor for tumor necrosis factor alpha expression. *Infection and Immunity*, 63(4), 1270-1277.

[23] http://science.jrank.org/pages/2612/Evolutionary-Change-Rate.html, first accessed 24 January 2012.

[24] Champion, M. (2011). http://www.news-medical.net/news/20110603/Mimicry-allows-bacteria-to-evade-hosts-defense-responses.aspx.

[25] Karimuribo, E., Mboera, L. E. G., Mbugi, E., Simba, A., Kivaria, F. M., Mmbuji, P., & Rweyemamu, MM. (2012). Are we prepared for emerging and re-emerging diseases? Experience and lessons from epidemics that occurred in Tanzania during the last five decades. *Tanzania Journal of Health Research*, 13(1), 1-14.

[26] Bhullar, K., Waglechner, N., Pawlowski, A., Koteva, K., Banks, E. D., Johnston, M. D., Barton, H. A., & Wright, G. D. (2012). Antibiotic Resistance Is Prevalent in an Isolated Cave Microbiome. *PLoS ONE*, 7(4), e34953.

[27] Schmid-Hempel, P. (2009). Immune defence, parasite evasion strategies and their relevance for 'macroscopic phenomena' such as virulence. *Philosophical Transactions of the Royal Society B*, 364, 85-98.

[28] Hisaeda, H., Yasutomo, K., & Himeno, K. (2005). Malaria: immune evasion by parasites. *The International Journal of Biochemistry and Cell Biology*, 37(4), 700-706.

[29] Sachs, J., & Malaney, P. (2002). The economic and social burden of malaria. *Nature*, 415, 680-685.

[30] Barry, A. E., Leliwa-Sytek, A., Tavul, L., Imrie, H., Migot-Nabias, F., Brown, S. M., Mc Vean, G. A. V., & Day, K. P. (2007). Population Genomics of the Immune Evasion (var) Genes of Plasmodium falciparum. *PLoS Pathogens*, 3(3), e34.

[31] Ferreira, M. U., Nunes, MD, & Wunderlich, G. (2004). Antigenic diversity and immune evasion by malaria parasites. *Clinical and Diagnostic Laboratory Immunology*, 11(6), 987-995.

[32] Gaschen, B., Taylor, J., Yusim, K., Foley, B., Gao, F., Lang, D., Novitsky, V., Haynes, B., Hahn, B. H., Bhattacharya, T., & Korber, B. (2002). Diversity considerations in HIV-1 vaccine selection. *Science*, 296, 2354-2360.

[33] Peek, R., Van Gool, T., Panchoe, D., Greve, S., Bus, E., & Resida, L. (2005). Drug resistance and genetic diversity of Plasmodium falciparum parasites from suriname. *American Journal of Tropical Medicine and Hygiene*, 73(5), 833-838.

[34] Harrington, W. E., Mutabingwa, T. K., Muehlenbachs, A., Sorensen, B., Bolla, M. C., Fried, M., & Duffy, P. E. (2009). Competitive facilitation of drug-resistant Plasmodium falciparum malaria parasites in pregnant women who receive preventive treatment. *Proceedings of the National Academy of Sciences*, 106(22), 9027-9032.

[35] Kidgell, C., Volkman, S. K., Daily, J., Borevitz, J. O., Plouffe, D., Zhou, Y., Johnson, J. R., Le Roch, K., Sarr, O., Ndir, O., Mboup, S., Batalov, S., Wirth, D. F., & Winzeler, E. A. (2006). A systematic map of genetic variation in Plasmodium falciparum. *PLoS Pathogens*, 2(6), e57.

[36] Romani, L. (2001). Overview of the fungal pathogens. *Kaufmann SHE, Sher A, Ahmed R. (eds.). Washington DC: ASM Press*, 25-37.

[37] Romani, L. (2004). Immunity to fungal infections. *Nature Reviews Immunology*, 4(1), 1-23.

[38] Marr, K. A., Patterson, T., & Denning, D. (2002). Aspergillosis: Pathogenesis, clinical manifestations, and therapy. *Infectious Disease Clinics of North America*, 16, 875-894.

[39] Fidel, P. L. Jr, & Sobel, JD. (1994). The role of cell-mediated immunity in candidiasis. *Trends in Microbiology*, 2, 202-206.

[40] Puccetti, P., Romani, L., & Bistoni, F. (1995). A Th1-Th2-like switch in candidiasis: new perspectives for therapy. *Trends Microbiol*, 3, 237-240.

[41] Abbas, A. K., & Lichtman, A. H. (2003). Cellular and Molecular Immunology. *Fifth Edition edn. Philadephia: Elsevier Science (USA)*.

[42] Chai, L. Y. A., Netea, M. G., Vonk, A. G., & Kulliberg-J, B. (2009). Fungal strategies for overcoming host innate immune response. *Medical Mycology*, 47, 227-236.

[43] Gauthier, G., & Klein, BS. (2008). Insights into Fungal Morphogenesis and Immune Evasion: Fungal conidia, when situated in mammalian lungs, may switch from mold to pathogenic yeasts or spore-forming spherules. *Microbe Washington DC*, 3(9), 416-423.

[44] Meiller, T. F., Hube, B., Schild, L., Shirtliff, M. E., Scheper, M. A., Winkler, R., Ton, A., & Jabra-Rizk, M. A. (2009). A Novel Immune Evasion Strategy of Candida albicans: Proteolytic cleavage of a salivary antimicrobial peptide. *PLoS ONE*, 4(4), e5039.

[45] Chamilos, G., & Kontoyiannis, D. P. (2005). Update on antifungal drug resistance mechanisms of Aspergillus fumigatus. *Drug Resistance Updates*, 8(6), 344-58.

[46] Pfaller, M. A., Moet, G. J., Messer, S. A., Jones, R. N., & Castanheira, M. (2011). Geographic Variations in Species Distribution and Echinocandin and Azole Antifungal Resistance Rates among Candida Bloodstream Infection Isolates: Report from the SENTRY Antimicrobial Surveillance Program (2008 to 2009). *Journal of Clinical Microbiology*, 49(1), 396-399.

[47] Balajee, S. A., Kano, R., Baddley, J. W., Moser, S. A., Marr, K. A., Alexander, B. D., Andes, D., Kontoyiannis, D. P., Perrone, G., Peterson, S., Brandt, M. E., Pappas, P. G., & Chiller, T. (2009). Molecular Identification of Aspergillus Species Collected for the Transplant-Associated Infection Surveillance Network. *Journal of Clinical Microbiology*, 47(10), 3138-3141.

[48] van der Linden, J. W. M., Warris, A., & Verweij, P. E. (2011). Aspergillus species intrinsically resistant to antifungal agents. *Medical Mycologyl*, 49(1), S82-S89.

[49] Amend, AS, Seifert, K. A., Samson, R., & Bruns, T. D. (2010). Indoor fungal composition is geographically patterned and more diverse in temperate zones than in the tropics. *Proceedings of the National Academy of Sciences*, 107(31), 13748-13753.

[50] Richardson, M., & Lass-Flörl, C. (2008). Changing epidemiology of systemic fungal infections. *Clinical Microbiology and Infection*, 14(4), 5-24.

[51] Cannon, R. D., Lamping, E., Holmes, A. R., Niimi, K., Baret, P. V., Keniya, M. V., Tanabe, K., Niimi, M., Goffeau, A., & Monk, B. C. (2009). Efflux-mediated antifungal drug resistance. *Clinical Microbiology Review*, 22(2), 291-321.

[52] Monk, B. C., & Goffeau, A. (2008). Outwitting multidrug resistance to antifungals. *Science*, 321, 367-369.

[53] Loeffler, L., & Stevens, D. A. (2003). Antifungal drug resistance. *Clinical Infectious Diseases*, 36(1), S31-41.

[54] Stevens, D. A., & Holmberg, K. (1999). Resistance to antifungal drugs: current status and clinical implications. *Current opinion in anti-infective investigational drugs*, 1, 306-317.

[55] Prasad, A. S. (1998). Zinc in human health: An update. *The Journal of Trace Elements in Experimental Medicine*, 11(2-3), 63-87.

[56] Prasad, A. S. (1998). Zinc and immunity. *Molecular and Cellular Biochemistry*, 188(1-2), 63-69.

[57] Prasad, A. S. (2008). Zinc in Human Health: Effect of Zinc on Immune Cells. *Molecular Medicine*, 14(5-6), 353-357.

[58] Mbugi, E. V., Meijerink, M., Veenemans, J., Jeurink, P. V., Mc Call, M., Olomi, R. M., Shao, J. F., Verhoef, H., & Savelkoul, H. F. J. (2010). Alterations in early cytokine-mediated immune responses to Plasmodium falciparum infection in Tanzanian children with mineral element deficiencies: a cross-sectional survey. *Malaria Journal*, 9(1), 130.

[59] Mbugi, E. V., Meijerink, M., Veenemans, J., Jeurink, P. V., Mc Call, M., Olomi, R. M., Shao, Chilongola. J. O., Verhoef, H., & Savelkoul, H. F. J. (2010). Effect of nutrient deficiencies on in vitro Th1 and Th2 cytokine response of peripheral blood mononuclear cells to Plasmodium falciparum infection. *Malaria Journal*, 9(1), 162.

[60] Savino, W., & Dardenne, M. (2010). Micronutrients and the immune system Nutritional imbalances and infections affect the thymus: consequences on T-cell-mediated immune responses. *Proceedings of the Nutrition Society*, 69, 636-643.

[61] Shvetsov, Y. B., Hernandez, B. Y., Wilkens, L. R., Thompson, P. J., Franke, AA, Zhu, X., & Goodman, M. T. (2010). Plasma Micronutrients and the Acquisition and Clearance of Anal Human Papillomavirus Infection: The Hawaii HPV Cohort Study. *Cancer Research*, 70(23), 9787-9797.

[62] Alexander, S., Maike, W., & Andreas, H. (2011). Micronutrients at the Interface Between Inflammation and Infection Ascorbic Acid and Calciferol. Part 1: General Overview with a Focus on Ascorbic Acid. *Inflammation and Allergy- Drug Targets*, 10(1), 54-63.

[63] Liu, Y., Jing, H., Wang, J., Zhang, R., Zhang, Y., Zhang, Y., Xu, Q., Yu, X., & Xue, C. (2011). Micronutrients decrease incidence of common infections in type 2 diabetes outpatients. *Asia Pacific Journal of Clinical Nutrition*, 20(3), 375-382.

[64] Taylor, C. E., & Camargo, C. A. Jr. (2011). Impact of micronutrients on respiratory infections. *Nutrition Reviews*, 69(5), 259-269.

[65] Veenemans, J., Mank, T., Ottenhof, M., Baidjoe, A., Mbugi, E. V., Demir, A. Y., Wielders, J. P. M., Savelkoul, H. F. J., & Verhoef, H. (2011). Protection against Diarrhea Associated with Giardia intestinalis Is Lost with Multi-Nutrient Supplementation: A Study in Tanzanian Children. *PLoS Neglected Tropical Diseases*, 5(6), e1158.

[66] Veenemans, J., Milligan, P., Prentice, A. M., Schouten, L. R., Inja, N., van der Heijden, A. C., De Boer, L. C., Jansen, E. J., Koopmans, A. E., Enthoven, W. T., Kraaijenhagen, R. J., Demir, A. Y., Uges, D. R., Mbugi, E. V., Savelkoul, H., & Verhoef, H. (2011). Effects of zinc and other micronutrients on malaria in Tanzanian children: a randomised trial. *PLoS Medicine*, 8(11), e1001125.

[67] Dekker, L. H., Fijnvandraat, K., Brabin, B. J., & van Hensbroek, M. B. (2012). Micronutrients and sickle cell disease, effects on growth, infection and vaso-occlusive crisis: A systematic review. *Pediatric Blood and Cancer*, 59(2), 211-215.

[68] Lahner, E., Persechino, S., & Annibale, B. (2012). Micronutrients (Other than iron) and Helicobacter pylori Infection: A Systematic Review. *Helicobacter*, 17(1), 1-15.

[69] Reilly, L., Nausch, N., Midzi, N., Mduluza, T., & Mutapi, F. (2012). Association between Micronutrients (Vitamin A, D, Iron) and Schistosome-Specific Cytokine Responses in Zimbabweans Exposed to Schistosoma haematobium. *Journal of Parasitology Research*, 2012, 1-9.