In this fascinating interview, Dr Sylviane Pied gives her take on the problems presented by malaria, and explains her work towards understanding the complex relationship between parasite, host and environment.

Why have you chosen India as your primary focus of investigation?

My first contact with India was during my postdoctoral position, which I chose to do in a country where malaria is transmitted. My preliminary studies were on the immune response to malaria for people in Gabon, in collaboration with Professor Maryvonne Kombila of the Centre Hospitalier de Libreville.

In India, the clinical pattern of malaria and ethnic signatures differ widely from that in Africa. In India, malaria is a mosaic of diseases with a multifaceted clinical phenotype. For instance, *Plasmodium falciparum* has re-emerged over this last decade, and severe malaria has consequently occurred in adults as well as children. The great majority of mortality is caused by multi-organ dysfunction associated with cerebral malaria. The involvement of these organs is also related to immunopathology. Clearly, this is not the same picture as the one found in Africa.

What types of environmental factors influence the pathology of a parasitic infection?

Parasite transmission is a dynamic process influenced by countless factors including changes in ecological and meteorological conditions, urbanisation, socioeconomic status, agricultural and cultural practices, population genetics, nutritional status, individual genetics and immunological factors. Other parameters, such as the great diversity of topography and climate even within one area, war, income of the country, public health policy and many more, also play a part in determining the prevalence and severity of the disease. For instance, malaria is transmitted to humans through the bite of infected female *Anopheles* mosquitoes during a blood meal. The wide genetic polymorphism of the parasite, the spread of drug resistance and the diversity of the vector species may also impact on disease outcome.

Has your research identified any differences in the epidemiology of parasitic diseases, particularly malaria, between India and Africa? Can you suggest what the main reasons are for these variations?

Differing sibling species, in particular the major species complex of the genus *Anopheles*, add to the complexity of malaria transmission; in the field, such diverse species are adapted to different climatic conditions and tend to become major vectors within specific zones in India and Africa. Thus, control strategies developed for one region might not necessarily be applicable for other regions of variable eco-epidemiological settings. Other factors to consider include the degree of drug resistance the parasites have achieved, the insecticide resistance of the vector and the highly adaptable nature of vector species.

Can you elaborate on how the host immune responses to malaria vary when the epidemiological environments differ between endemic and epidemic, urban and rural?

We can postulate that the outcome of the infection would be the result of mutual interactions between the harmful (pathological) and helpful (protective) responses. Nevertheless, the conditions and disturbances governing commitment to either protection or pathology, and mechanisms involved in the control of the balance between these two sets of responses, are still unknown. These two types of response would be greatly influenced by the pathogen, the immunological experience, the genetic background of the populations, epigenetic and environmental factors such as transmission intensity. However, as with many infectious pathological situations, severe disease due to parasite infection can also be the result of deleterious unregulated immune responses rather than direct pathogenic consequences of the infectious agent. This is particularly true in the case of T-cell responses during parasitic infections, which emphasises the need for thorough host-pathogen immunophysiopathological studies. Such considerations have an important bearing on therapeutic intervention and vaccine development.
Trying the triangle

A Franco-Indian consortium, the International Associated Laboratory on Systems Immunology and Genetics of Infectious Diseases, has been working towards understanding malaria by making use of the disease triangle model.

THE DISEASE TRIANGLE model is a simple concept for determining an individual's resistance to disease. Developed in 1960, the model relies on the fact that three factors are required for disease vulnerability: a hazardous pathogen, a susceptible host and a conducive environment. The model provides a useful framework through which to predict whether a host will be receptive to a disease or resistant to it. Since its formalisation, the disease triangle model has emerged as an excellent tool for predicting, limiting and controlling epidemics; the socioeconomic impact of its success has been huge. There is one problem; it has only ever been applied to plants. Surprising as it may seem, the highly effective triangle model has been entirely ignored in the context of infectious diseases in humans.

One needs only to look at a map of malaria endemic zones to see how dependent the disease is on environmental factors. Malaria is classically a tropical disease, and anyone familiar with it as a health concern will be aware of the high-risk band running around the equator, throughout the tropics and into Southeast Asia. This is a powerful indication of the disease's geographical specificity on a large scale, but it is also highly specific at the country and regional level. Considering malaria prevalence in Ethiopia, for example, it is possible to identify endemic areas of perhaps 50 square miles that neighbour similar regions with no malaria at all. Equally, studies have shown that individual genetic factors – on the part of the host and the parasite – can make a great difference to disease susceptibility.

A DISEASE WITH MANY FACES

The problem with developing universal control strategies, treatments or a vaccine for malaria is that the interaction of these three factors determines the characteristics of the disease. With such a high level of variation it is unlikely that approaches which prove effective in Africa will be helpful in India. In fact, there is no guarantee that a useful treatment developed in one region of Ethiopia will even be viable in a neighbouring area. The key to overcoming this problem could be a new formulation of the disease triangle model. Only by thoroughly examining all of these parameters can scientists better understand malaria and how to effectively reduce its associated morbidity and mortality.

One consortium – the International Associated Laboratory on Systems Immunology and Genetics of Infectious Diseases (LIA SIGID) – is composed of scientists from France and India who are working towards understanding the pathophysiology of malaria in India on this basis. The French participants are based at the French National Centre for Scientific Research (CNRS), French Institute of Health and Medical Research (INSERM), Institut Pasteur Lille, Université Lille and the Université Pierre et Marie Curie. Whereas the Indian contributors work from institutions funded by the Indian Ministry of Science and Technology’s Department of Biotechnology – the Institute of Life Sciences, the National Institute of Immunology and the National Center of Cell Sciences – in addition to the Tata Institute of Fundamental Research, Ispat General Hospital and SCB Medical College.

Between them, these scientists hope to bring a new approach, as well as sustained bioinformatics research, to the accurate characterisation of malaria, which might subsequently lead to more accurate methods of predicting infection outcome. French coordinator of the SIGID programme, Dr Sylviane Pied from CNRS, describes: "The purpose of establishing this consortium is to promote and enhance the scientific interactions through pooling of resources and to foster the enhanced scientific and technical manpower exchange for training and knowledge upgradation". She works in close collaboration with the Indian coordinator Dr Balachandran Ravindran from the Institute of Life Sciences in Bhubaneswar.

METHODS AGAINST MALARIA

SIGID's work begins with a wide variety of approaches for identifying the immune and genetic signatures of patients that are linked to the various possible expressions of malaria. Transcriptomic,
INTRODUCTION

THE DISEASE TRIANGLE MODEL

The disease triangle model integrates the additive role of environment, vector, parasite and host interactions in parasitic diseases. To use a modified ‘disease triangle model’ as an holistic approach to better understand the additive role of environment, vector, parasite and host interactions in parasitic diseases.

OBJECTIVES

To elucidate the relationship between the adaptive parasite and the adaptive host immune responses to two brain autoantigens, depending on their location: either α-1-spectrin in Gabon, Africa, or β-tubulin-3 in Gondia, Maharashtra state, India. These autoantibodies were correlated positively with increased cytokine levels that have been previously associated with cerebral malaria, and the findings suggest the involvement of immunophysiological processes in malaria.

These findings are just the start. In the context of SIGID, these studies will be extended to include several cohorts of infected patients recruited from two well-characterised populations living in different environments within the Indian state of Orissa. In addition, patients from an urban epidemic area will be recruited in Mumbai city.

LEARNING OPPORTUNITIES

In addition to conducting important research into parasitic diseases the SIGID group will promote the training of scientists and students, as well as fostering international science links. The project will bring together scientists from a wide range of fields – infectious disease, parasitology, microbiology, immunology, statistics, computer science and mathematics – each using their own experimental processes, and developing experience while working together towards a common goal. International links between France and India will be a natural part of the work’s progression, and the scientific and educational environment promoted by these links may lead to new approaches.

It is hoped that SIGID will also facilitate student cross-training within international integrated Master’s-PhD programmes on Immunology, Genetics and the Systems Biology of Infectious Diseases. The objective of these programmes is to provide students with a detailed knowledge of the state-of-the-art approaches used in the developing fields of systems biology, genomics and integrative immunology as applied to infectious diseases, and to allow them to acquire the methodological expertise essential for conducting a whole research project. This is a highly ambitious goal in terms of education, but in that sense, it matches up with the overall ambition demonstrated by the SIGID project as a whole.

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