More than 60 years have passed since J B S Haldane first suggested that the unusual distribution of Cooley’s anaemia, the disorder now recognised as β-thalassaemia, might be explained by malaria. In a landmark report published in 1949 he noted that the “corpuscles of the anaemic heterozygotes are smaller than normal, and more resistant to hypotonic solutions”. Haldane also speculated that such corpuscles “are also more resistant to attacks by the sporozoa which cause malaria, a disease prevalent in Italy, Sicily and Greece, where the gene is frequent”. Since then, Haldane’s malaria hypothesis has been extended to a wide range of inherited disorders of haemoglobin, which are known collectively as the haemoglobinopathies. In The Lancet Infectious Diseases, Steve Taylor and colleagues present an up-to-date systematic review of clinical studies that have assessed the effect of these disorders on risk of malaria in different populations. Their study serves two main purposes. First, it provides compelling evidence that Haldane’s original hypothesis was correct. Second, and equally importantly, it emphasises some of the important gaps in our knowledge and the need for further studies in this area.

Haemoglobinopathies fall into two main categories: structurally variant forms of haemoglobin, such as haemoglobin S and haemoglobin C (the common causes of sickle-cell disease); and thalassaemias, which are disorders characterised by reduced or absent production of either α-globin or β-globin molecules that combine to form normal adult haemoglobin A. Although heterozygous carriers have essentially no phenotypic traits, homozygous carriers of some haemoglobinopathies, such as haemoglobin S and β-thalassaemia, have chronic ill health and die prematurely. As such, these haemoglobinopathies are classic examples of balanced polymorphisms—disorders for which the frequency in populations results from a balance between positive selection for heterozygotes (through a fitness advantage) and negative selection for homozygotes (through a fitness disadvantage).

The evidence that malaria selects for the haemoglobinopathies comes from various sources. The geographical distribution of many of these genetic disorders is the same as the historical distribution of malaria, which remains the case at global and regional scales. Moreover, the genetic structure of many haemoglobinopathies suggests that disorders of broadly similar phenotype have arisen, and been selected for, from more than one genetic origin. However, the best proof comes from clinical studies such as those summarised by Taylor and colleagues. Their meta-analysis shows conclusively that several of the haemoglobinopathies confer significant degrees of protection against severe forms of clinical Plasmodium falciparum malaria, which is associated with the highest global burden of disease and most deaths. However, the study also shows how little is understood about Haldane’s malaria hypothesis more than 60 years after it was first published. Taylor and colleagues could identify only 62 studies that reported the quantitative effects of haemoglobin S, haemoglobin C, or α-thalassaemia on various aspects of clinical malaria. None of these studies reported on malaria-specific deaths, few addressed β-thalassaemia or haemoglobin E (important diseases that affect millions of people worldwide), and few assessed other species of malaria or important questions such as malaria in pregnancy or birth outcomes. Finally, although not the main aim of the report, it also makes clear that the mechanisms by which the haemoglobinopathies result in malaria protection are incompletely understood.

Addressing such problems conclusively is difficult. For example, rates of malaria transmission are now so low in much of south and southeast Asia that a large investment would be needed to investigate the effects of some disorders (including haemoglobin E and β-thalassaemia) in conditions of natural exposure. Moreover, different polymorphisms might interact to have unpredictable effects on malaria-protective mechanisms, so the broad haplotype of study participants must be taken into consideration. Finally, numerous investigators have suggested that the effects of some haemoglobinopathies might not be entirely specific to malaria. For example, a protective effect of α-thalassaemia against non-malaria diseases has been reported in several studies, although how this might be mediated is an open question.

Despite such challenges, development of a clear picture of the extent to which specific haemoglobinopathies protect against different forms of clinical malaria, and the mechanisms behind protection, is an important exercise. Malaria continues to place an intolerable burden on the
world’s most vulnerable populations.\(^4\) Learning how human beings have adapted to survive this terrible disease could yet yield clues that lead to a permanent solution.

Thomas N Williams
University of Oxford, Nuffield Department of Medicine, Centre for Vaccinology and Tropical Medicine, Oxford OX3 9DU, UK
tom.n.williams@gmail.com
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Pharmaceutical quality: an urgent and unresolved issue

Selling of substandard and counterfeit drugs has been an issue ever since an early herbalist’s assistant noted that one pile of dry herbs looked much like another. The only changes have been the increasing expertise and extent of the problem. The international response to counterfeit drugs began with a 1988 World Health Assembly resolution that called for WHO to help prevent and detect the spread of so-called substandard/spurious/falsely-labelled/falsified/counterfeit drugs.\(^1\) This and subsequent resolutions culminated in an international meeting in 2006, which resulted in the Declaration of Rome\(^2\) and the International Medical Products Anti-Counterfeiting Taskforce (IMPACT).\(^3\) The casual observer would be forgiven for believing that this high-level action means that the issue is under control; unfortunately, as Gaurvika Nayyar and colleagues\(^4\) emphasise in *The Lancet Infectious Diseases*, this belief is far from the case. The investigators discuss some of the major factors associated with the control of counterfeit and substandard drugs and, importantly, offer clear recommendations to guide future actions against this threat to the legitimate drug supply.

Research is insufficient to clarify the extent or cause of poor drug quality. In a large review,\(^5\) Newton and colleagues were able to find only one study that combined random sampling with an adequate description of methods. Importantly, no large randomised studies of drug quality have been done in either China or India. Because roughly a third of the world’s population lives in these countries, and they are probably the source of many counterfeit drugs, global estimates should be seriously examined.

The criminal aspect of counterfeiting makes it a more interesting topic than quality control, but counterfeiting is only one cause of poor drug quality, and probably not the most substantial.\(^6\) In practice, drug quality is dependent on the overlapping effects of poor manufacturing standards, criminal counterfeiting, adulteration with inactive or toxic fillers, relabelling of time-expired drugs, and degradation during storage.\(^7\) Reliable research concerning counterfeiting is limited, and almost no information is available about the other four factors.\(^8\) The only pilot studies\(^9,10\) of drug quality in India noted many substandard drugs, but no evidence of counterfeiting.

Finally, there is no agreement about basic definitions. This issue is complex, but for international trade purposes, counterfeit refers to the unauthorised use of a trademark. Different interpretations of the word counterfeit can result in generic drugs being branded as illegal and sometimes confiscated.\(^11\) Construction of a balance between protection of intellectual property and the maintenance of drug quality has plagued the relation between WHO and IMPACT to the extent that IMPACT has now moved its secretariat from Geneva and relocated to Italy.\(^12\)

Nayyar and colleagues’ recommendations will hopefully spark a broad debate about this fundamental issue. At the very least, substantive progress against poor quality drugs needs several interventions. Accurate research is urgently needed with comparable...