

# Haemochromatosis: Phenotype to genotype or man to molecules

**P Jacobs,<sup>1</sup>** MB BCh, MD, PhD (Med), DSc (Med Sci), FRCP (Edin), MACP, FCP (SA), FRCPath (UK), IFCAP, MASSAf, FRSSAf, **L Wood,<sup>2</sup>** FRCP (Edin), BA (Nursing Science), MSc (Med) (Haematol), RN, RM, Diploma in Intensive Nursing Care, Ward Administration and Clinical Teaching

<sup>1</sup>*Emeritus Professor of Haematology, University of Cape Town, Honorary Consultant Physician, Groote Schuur Hospitals Teaching Group, Cape Town, Professor of Internal Medicine, University of Nebraska Medical Center, USA, Professor Extraordinaire in Haematological Pathology, Stellenbosch University and Tygerberg Academic Hospital, Parow, Cape Town, and The Haematology Research Group, PathCare, Cape Town, South Africa*

<sup>2</sup>*Medical Biological Scientist, Senior Lecturer Extraordinaire in Clinical Haematology, Stellenbosch University and Tygerberg Academic Hospital, Parow, Cape Town, and The Haematology Research Group, PathCare, Cape Town, South Africa*

**Corresponding author:** P Jacobs ([jill.hughes@pathcare.co.za](mailto:jill.hughes@pathcare.co.za))

This is the third in our vignettes that are centred on everyday clinical presentations. Each emphasises practical aspects of team-based care that are applicable to general practitioners, specialists and paramedical professionals alike.

Iron-overload syndromes, whether genetically or environmentally determined, increase morbidity and mortality. Familial haemochromatosis, as the prototype, may have a prolonged subclinical phase before presenting with dermatological, hepatic, pancreatic, cardiac, musculoskeletal or endocrine symptoms and signs. Improved understanding of iron metabolism, coupled with genetic testing, underlines current approaches to screening, diagnosis and proactive multidisciplinary management encompassing appropriate family studies.

These changed circumstances strongly emphasise the need for much wider appreciation of hazards associated with accumulation of this trace metal above physiological limits and benefits of early, or pre-emptive, correction.

## Introduction

Disorders of the blood cause some of the commonest symptoms and signs for which patients seek medical advice. A carefully taken history and meticulous physical examination, complemented by thoughtful and judicious use of laboratory tests, provide the clinical basis for a working diagnosis. Specialised haematology may be needed to extend evaluation to the bone marrow and plasma while supplementary imaging and radionuclide technology further link primary care practitioner or specialist to the experienced haematologist. Such a multidisciplinary and fully integrative approach offers the preferred way to problem solving and optimum management.

Under normal circumstances iron is an essential element for survival of plants, microbes and higher animals. Its life-sustaining properties play a central role in gas transfer and electron transport, catalysing oxidative metabolism, contributing to cell growth, proliferation<sup>[1]</sup> and occupying an important role at the host-pathogen interface.<sup>[2]</sup> Body iron reserves are regulated by absorption at the level of the upper small bowel. The master regulator of these pathways is hepcidin – a peptide of liver origin.<sup>[3]</sup>

Any excessive accumulation in storage sites, primarily the hepatic parenchyma and reticuloendothelial cells, is shown by raised ferritin levels and percentage saturation of transferrin. The consequences are acceleration of free radical reactions, causing cellular injury and organ dysfunction which is progressive and often irreversible.<sup>[4]</sup> These phenomena may be primary or genetically determined. In contrast, secondary causes bypass the governing mechanism in the gastrointestinal tract, for example transfusional siderosis.<sup>[5]</sup>

The classic example of iron overload syndromes are the haemochromatosis syndromes.<sup>[6]</sup> These are characterised by a

distinctive increase in skin pigmentation associated with hepatic, pancreatic, cardiac, musculoskeletal and endocrine failure and specific neurological abnormalities.<sup>[7-9]</sup>

The primarily biochemical disruptions of diabetes mellitus, cardiovascular disease, arthritis and a range of endocrine disorders may also contribute to these syndromes.<sup>[10]</sup> In such situations diagnosis and treatment by phlebotomy to reduce excess can blunt subclinical tissue damage and there are data to show survival benefit, although reversibility in affected organs is not clearly defined. As a result it is important for all medical practitioners to be aware of haemochromatosis and its risk factors and to start treatment as early as possible.

## Physiology

### Absorption

Dietary iron is *extracted* into duodenal enterocytes at the luminal or villous pole via the divalent metal transporter 1 (DMT 1). When dietary iron is digested, the metal is released and then converted from ferric to ferrous form. When iron is presented as the haem complex, transport depends upon a separate carrier protein (HCP 1)<sup>[3,4]</sup> (Fig. 1).

### Enterocyte export

*Passage* into the circulation takes place at the basal or serosal surface through the transmembrane structure, ferroportin, where function is regulated by hepcidin.<sup>[11,12]</sup> The latter peptide is produced by the liver and, having antimicrobial properties, is a component of the innate immune system. This peptide is known to be the key homeostatic regulator for iron. Function is modulated by other proteins under the control of genes for haemochromatosis (HFE) heemojuvelin and transferrin receptor 2.<sup>[6]</sup>

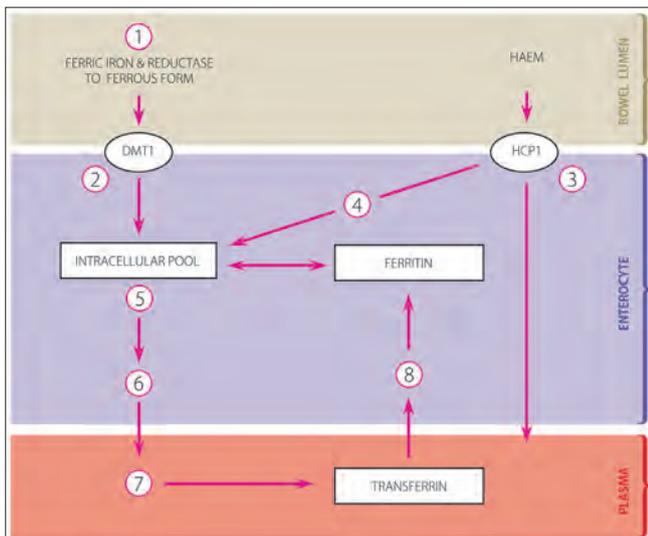


Fig. 1. The major enterocyte pathways for absorption. Dietary iron in the bowel is reduced to the ferrous form via a reductase (1) and then passes into the enterocyte by the divalent metal transporter DMT1 (2). Haem iron is handled through a different carrier – HCP1 (3). Once within the cytoplasm (4) joins the non-haem iron pathway or handled as haem moving to plasma (5). Excess is stored as ferritin whereas that required for physiological purposes is first oxidised by hephaestin (6) and then exported into the plasma via ferroportin (7). In contrast to this hepcidin model is that for crypt programming, thought to be operating concurrently (8).<sup>[3]</sup>

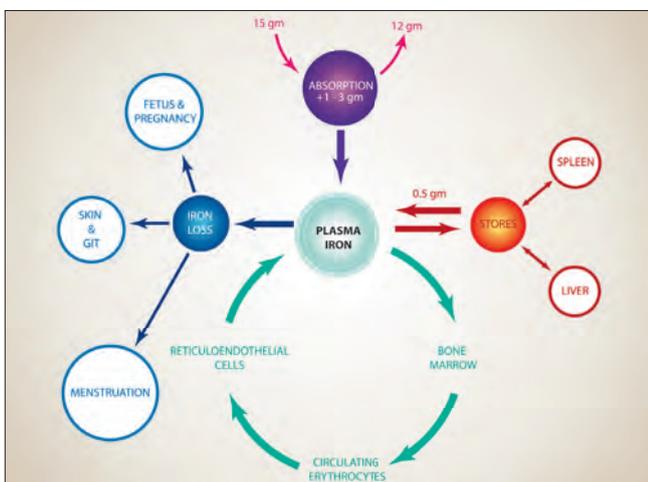


Fig. 2. Physiology of body iron exchange. The daily loss to the external environment is small, being between 1 mg and 3 mg primarily from desquamation of skin and gastrointestinal tract cells balanced by recovery from the diet. However, internal iron movement, mainly for haemoglobin synthesis, is up to 40 mg in 24 hours. Such rapid recycling through the plasma reflects the relatively large quantities of the metal released from red cell breakdown in the reticuloendothelial system that is being transported back to developing erythroid precursors in the marrow. In women compensation is made for pregnancy and menstruation. The storage compartment, comprising ferritin and to a lesser extent haemosiderin, is located in hepatocytes and macrophages in liver, spleen, bone marrow as well as muscle.<sup>[6]</sup>

Precisely the same mechanism operates at the level of the reticulum cell or macrophage, allowing re-utilisation or recycling of the iron recovered

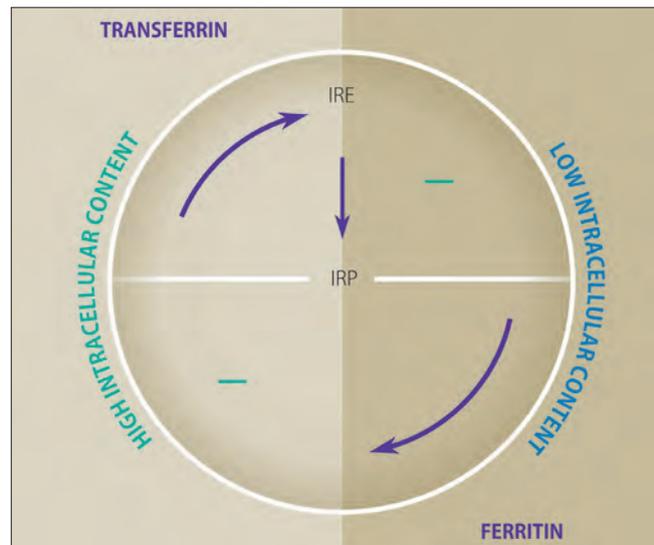


Fig. 3. The ferrostat. In contrast to cellular egress, regulated by hepcidin, uptake and storage are controlled by synthesis of transferrin receptors and ferritin. The latter two pathways are coordinated by a pair of iron-regulating proteins, designated IRP 1 and IRP 2. There is up- or down-regulation, reciprocally via mRNA for the two proteins which they code, by iron-responsive elements in respective transcripts (IRE). Thus, when the iron pool is decreased the two options counterbalance in favour of reducing retention, and vice versa.<sup>[10]</sup>

once old red cells have been removed from circulation and degraded, with temporary storage in ferritin or haemosiderin (Fig. 2).<sup>[4,5]</sup>

### The ferrostat

Cellular uptake and storage are governed by the synthesis of transferrin and ferritin. These combined processes are co-ordinated by the iron regulatory proteins that, when intracellular levels or pool are low, engage corresponding iron responsive elements in the transferrin receptor mRNA with up-regulation and ingress of iron from plasma. At the same time, retention in ferritin falls, so releasing more iron into the circulation, with reduced storage of redundant amounts both in this protein and as haemosiderin. The reverse arrangement is found when iron within cells is increased<sup>[10]</sup> (Fig. 3).

### Transport

#### Internal iron kinetics

Iron is primarily transported to the developing red cell mass or erythron in the marrow. Delivery is via transferrin, which is the specialised transport protein in the plasma, to the corresponding receptors on the cell surface or membrane (Fig. 2).<sup>[3,4]</sup>

Smaller amounts are available for biosynthesis of metalloproteins or enzymes, as well as delivery to the crypts in the bowel, where intracellular concentrations moderate absorption. It is likely that both this model<sup>[3]</sup> and that focusing on hepcidin<sup>[9,11,12]</sup> function interactively (Fig. 1).

### Pathophysiology of overload syndromes

#### Definition

An increase in the supply of iron to more than that required gradually expands stores, leading to progressive functional disturbance and

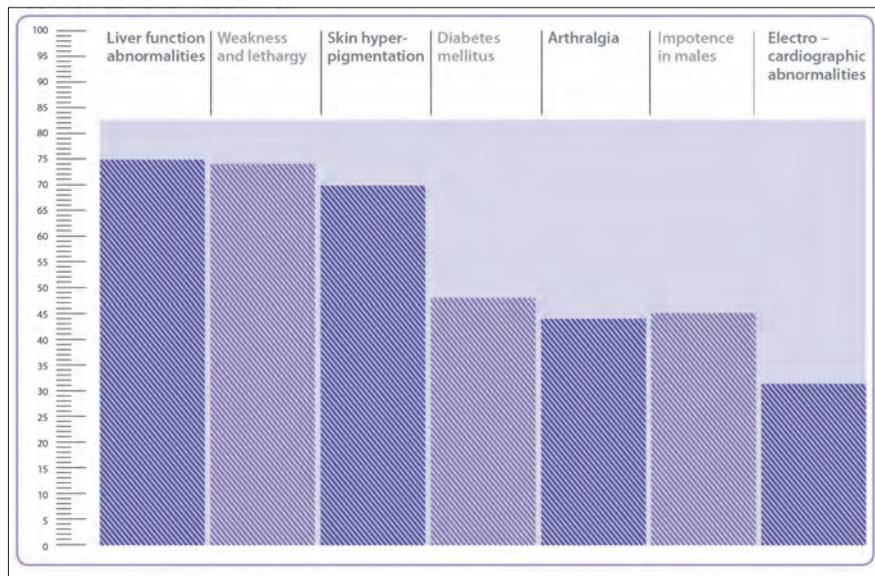


Fig. 4. Common clinical presentation.<sup>[14]</sup> This profile of characteristics has been altered by the now much wider availability and increasing use of the biochemical screening studies that bring to light otherwise occult or silent increases in body iron stores reflected in raised percentage of transferrin and increased plasma ferritin levels.<sup>[14]</sup>

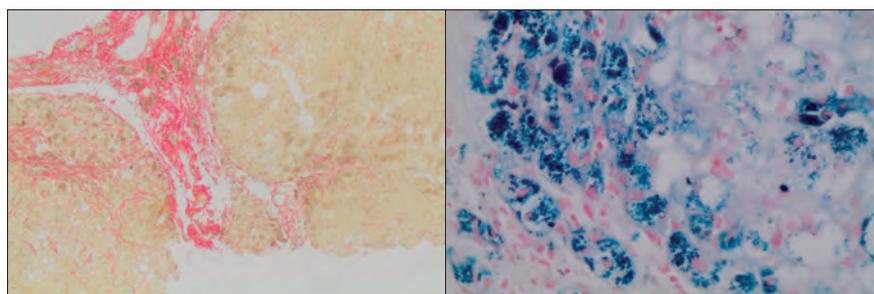


Fig. 5. Liver biopsy showing cirrhosis and iron overload. There are two striking histopathological features on liver biopsy. The first is an increase in fibrous tissue and nodularity highlighted by the Sirius red stain (left panel). The second is dense deposition of iron in hepatocytes revealed by the Perl's reaction (right panel). (Courtesy of Dr Kathy Taylor, PathCare.)

cumulative anatomical change in target organs. The pattern is rate and magnitude dependent. Individual manifestations vary with genetic prevalence and penetrance.<sup>[5,7]</sup>

**Classification**

**Primary**

In primary syndromes the fault lies in the regulation of absorption due to mutations, with quantitative or qualitative defects in hepcidin or in other genes that determine unbalanced accumulation from the external environment, giving rise to the classic familial variants.<sup>[5,10]</sup>

**Secondary**

Secondary syndromes are a result of lesions in other systems including ineffective erythropoiesis, chronic liver disease or porphyria when occurrence is sporadic.<sup>[10]</sup>

**Clinical manifestations – phenotype**

Fig. 4 depicts the common clinical presentation of haemochromatosis.

There is some phenotypic variation with haemojuvelin, hepcidin or ferroportin mutations presenting at an earlier age. In these cases cardiomyopathy and endocrine defects are prominent. In contrast, involvement of haemochromatosis or the transferrin receptor is seen later, usually with more liver disease.<sup>[5]</sup>

Incidental diagnosis typically occurs when blood tests are undertaken to evaluate nonspecific fatigue that then reveal increases in ferritin or percentage saturation of transferrin.<sup>[13]</sup>

Classically, skin pigmentation occurs, typically called 'bronze', although a bluish-grey colour is more appropriate.<sup>[14]</sup>

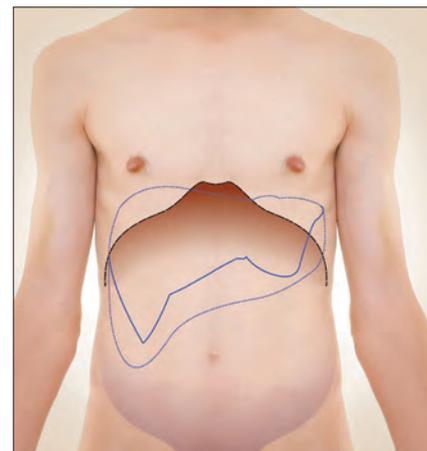


Fig. 6. Hepatomegaly. Varying degrees of increasing liver size may initially be noted only on clinical examination. The shaded area is palpable hepatomegaly — this may be much greater, as in dotted limits. With time cirrhosis results in contraction, size reduces and may no longer be evident. It is at those late stages that portal hypertension occurs with ascites and variceal bleeding.

Liver function tests may be abnormal, whereas scleral icterus and varying degrees of hepatomegaly are later and more ominous signs, correlating with considerable expansion of iron stores (Fig. 5) and cirrhosis, progressing relentlessly to portal hypertension (Fig. 6).<sup>[14]</sup>

Cardiomyopathy not infrequently precedes clinical diagnosis. The first warning may be supraventricular arrhythmias that may be lethal. With longer duration of iron deposition in the myocardium restrictive patterns emerge, leading to symptomatic congestive cardiac failure as a late consequence.<sup>[15,16]</sup>

There is increasing evidence that accelerated coronary artery disease due to atherosclerosis with ischaemia is a further hazard.<sup>[17]</sup>

Diabetes, which may be either type 1 or type 2, can predate clinical diagnosis and should be excluded in all patients presenting with haemochromatosis.<sup>[18-20]</sup> Similarly, hypertriglyceridaemia may be present,<sup>[21]</sup> adding the risk of ischaemic damage to restrictive cardiomyopathy that is a result of iron accumulation in the myocardium.

These patients frequently have pituitary, thyroid or adrenocortical insufficiency.



Fig. 7. Radiological abnormalities. Severe osteoarthritic changes may occur early and are uniquely located in the second and third metacarpophalangeal joints (left panel). Surprising degrees of skeletal demineralisation accumulate and may result in incapacitating osteoporosis with osteoarthritis seen in this teenager with the juvenile variant (right panel). (Courtesy of Dr Derek Solomon, Tuft and Partners.)

**Table 1. General management principles**<sup>[92,33]</sup>

Aggressive phlebotomy – donor programme
Iron chelation as a second alternative
Essential to prevent complication – serious organ damage
Hepatocellular carcinoma
Hypogonadism – cirrhosis – destructive arthritis
Insulin-dependent diabetes
Skeletal injury

Testicular atrophy is also well known. Careful history will reveal amenorrhoea, and sexual dysfunction in both sexes.<sup>[5,7,9]</sup>

Arthropathy, especially when atypical, may be early onset and another marker of tissue injury. This typically occurs in the carpal and

metacarpal joints, particularly symmetrical involvement of the thumb, index and forefingers. Osteoporosis is common (Fig. 7).<sup>[22]</sup>

Myths abound and lead to widespread anxiety. It is prudent to anticipate such disinformation and proactively provide reliable reassurance for each case.<sup>[23]</sup>

### Biochemical manifestations – genotype

#### Type 1 – mutations in HFE gene

This hereditary entity is the most common genetic disorder in persons of Northern European descent, with the C282Y mutation being a strong predictor for haemochromatosis.<sup>[5,24–26]</sup> Approximately 0.44% of those with the disease are homozygous for this mutation, with around 10% heterozygous. Figures are for the USA and corresponding data for South Africa are not available. The H63D mutation is more prevalent but has a milder phenotype.

The protein product from this gene regulates hepcidin expression and missense mutations decrease production, resulting in excess iron moving from the gastrointestinal tract into the circulation. This is most prominent in the homozygotes, leading to parenchymal deposition initially in liver but subsequently

in the pancreas, heart and other organs. The same phenomenon is evident but less severe in the heterozygotes.<sup>[13]</sup>

#### Type 2 – mutations in haemojuvelin gene

This is a severe autosomal recessive condition, leading to early and profound overload with two subtypes – the first involving the hepcidin regulatory protein known as haemojuvelin. In the second the mutation is in the hepcidin gene itself.

#### Type 3 – mutations in transferrin receptor 2

This is a rare autosomal defect producing heavy deposition in early life although it is less aggressive than type 2.

#### Type 4 – mutations in the ferroportin gene

This is described as atypical haemochromatosis and is inherited as an autosomal dominant condition. The normally encoded protein regulates enterocyte export in response to hepcidin, while the mutant is resistant to internalisation and degradation, resulting in unregulated iron absorption. Two subtypes are recognised. The first has relatively low transferrin saturation with deposition primarily in the reticuloendothelial system. The second resembles the traditional HFE phenotype targeting the hepatocyte for initial deposition.<sup>[27]</sup>

Non-genetic causes may reflect environmental injury, typically from increased dietary or parental sources.

### Laboratory studies

#### Screening

Biochemically this should be selective and restricted to patients with unexplained liver disease, endocrinology or carpal arthropathy. It is particularly useful in first-degree relatives of diagnosed cases.<sup>[13,18]</sup> Iron overload is present when serum transferrin saturation is initially above 45% in women and 50% in men.<sup>[20]</sup>

Serum ferritin levels over 300 ng/ml indicate increase in stores, although there is debate about the actual level at which studies should be undertaken. Targeted screening focuses on those with a familial history of liver disorders, otherwise unexplained cardiac disease, arthropathy or endocrinopathy, especially diabetes or male sexual dysfunction.<sup>[18,22]</sup>

## Diagnosis

Molecular genetics is well established in diagnosis. The HFE mutations are typically C282Y and H63D, although this will vary geographically.<sup>[10,25]</sup>

Iron overload can be determined in selected patients by liver biopsy although this is usually limited to obtaining information about tissue injury such as cirrhosis. Less invasive alternatives are modern radiological techniques.<sup>[28,29]</sup> These include quantitative magnetic resonance imaging (MRI) and sophisticated research methods that are not readily available, such as SQUID or biomagnetic liver susceptometry and transverse magnetic relaxation rate.

## General management principles (Table 1)

### Phlebotomy

Early diagnosis and comprehensive management programmes are essential to avoid iron-related tissue injury with emphasis on regular monitoring of iron status and the high index of suspicion for late-presenting complications that may occur despite reduction in body stores. Bloodletting was the treatment proposed in 1950. By 1969 this had become established as an effective means of improving survival. This is an inexpensive and readily available intervention and the blood can be used by the transfusion services.<sup>[30]</sup>

### Chelation

This possibility appeared attractive but is inconvenient and uncomfortable for patients. Initially, only parenteral agents were available. However, new and highly effective oral alternatives are being evaluated both in place of, and in association with, venesection.<sup>[31-33]</sup>

### Innovative options

An understanding of the role of low hepcidin levels in the pathogenesis of iron overload has led to research into replacement of this peptide. Early studies are encouraging.<sup>[34]</sup>

### Reversibility

The outlook for many of these individuals, particularly when diagnosed before structural changes such as cirrhosis have occurred, has continued to improve. Reduction of iron prevents the progression of associated damage to many organs and reversibility has

been noted in diabetes. However, reversibility in skeletal injury is less impressive. This observation should be tempered with the realisation that long-term follow-up is only just becoming available and in no way detracts from aggressive approaches to reduce injurious concentrations of the trace metal in many tissues.

## Summary and recommendations

Accumulating experience over the last five decades has clearly shown the benefits of early diagnosis of iron depletion and treatment through venesection. This principle remains both cost-effective and beneficial for the cardiovascular system and holds promise for atherogenesis. Furthermore, metabolic defects, primarily diabetes, undergo variable degrees of improvement, and replacement therapy for endocrinology contributes to improved quality and quantity of life. These diseases are anticipated to benefit significantly from more targeted therapy, for example of hepcidin replacement, and have been the model for investigating patients with hypertriglyceridaemia where iron overload may uncommonly be responsible. Finally, entering the era of gene therapy, and with the capacity to identify mutations, the possibility of engineering and permanent correction is no longer as remote as previously seemed to be the case.

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## SINGLE SUTURE

### Coronavirus threat

'Can transmit from person to person'. That is how the World Health Organization is now talking of the coronavirus that emerged last year in the Middle East.

Clusters of people with the viral infection, dubbed Middle East respiratory syndrome (MERS), give evidence that it can spread. What's more, France's health ministry has reported that a man who fell seriously ill with MERS after a trip to Dubai passed the virus to the person in the next hospital bed. But the virus has not spread widely in the community and close contact appears to be necessary for transmission, says Keiji Fukuda of the WHO.

However, Fukuda notes that undiagnosed cases may exist, with only mild symptoms. The two earliest known cases were part of a cluster of respiratory infections in April 2012 in Jordan. The others were milder and are thought to have been due to the virus, even though standard tests were negative. Routine tests on the first French patient were also negative, only deep lung sampling uncovered the virus.

Virologists are now working on a test for viral antibodies that can show if someone was infected in the past. That could reveal how widespread the virus really is.