

will limit the usefulness of this technique in many clinical settings in developing countries. The widespread use of the string test as reported by Vargus and colleagues will similarly be hampered by the need for sputum induction and culture of the specimen.

To improve the diagnosis of tuberculosis in children in developing countries, the availability of a simple rapid non-invasive test that can be done at health centres would be ideal. Various serological tests have been evaluated but, because of the low sensitivity and specificity of these tests under clinical conditions, they are not useful for diagnosing tuberculosis in children.¹⁰ The finding that the ELISPOT test¹ was workable in a district hospital by a paediatrician with minimal training and that it has greater sensitivity than the tuberculin skin-test in detecting tuberculosis infection provides the possibility for improved diagnosis of paediatric tuberculosis, especially in settings with high HIV-infection rates. In its current form, however, with the need for a microscope, centrifuge, and incubator, this test will have limited usefulness in smaller health centres without such equipment.

The paediatric tuberculosis score-chart was developed to provide a simple method for diagnosing tuberculosis in resource-limited settings. These charts have low sensitivity and specificity, especially in areas with high rates of HIV¹¹ and hence are of limited value.

The development of a simple affordable dipstick test in whole blood that can detect tuberculosis infection in the HIV-infected infant and child will greatly improve the ability of health-care staff to provide appropriate treatment and avoid the inappropriate use of antibiotics. This situation is not a pipe dream when we consider the available resources for tuberculosis and HIV research and the current efforts in developing new diagnostics for tuberculosis. The Foundation for Innovative New Diagnostics (FIND), an independent not-for-profit foundation launched in 2003 by the Special Programme for Research and Training in Tropical Disease with funding from the Gates Foundation, has chosen tuberculosis as its first target. Several innovative and rapid tests are being developed with the support of FIND. The development of improved tools for the diagnosis

of tuberculosis is one of the research goals of the National Institutes of Health in the USA.

Someone in the world is infected with the tuberculosis bacillus every second, and someone dies from tuberculosis every 15 seconds, one out of every three being a child.¹² Sombre statistics, but not irreversible with the combined effort of scientists, funding bodies, public-health practitioners, and national governments in the search for improved diagnostics and treatment for tuberculosis.

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Revising the immunological theories of asthma and allergy

See *Mechanisms of Disease*
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In this issue of *The Lancet*, T Heaton and colleagues examine the immunological foundations of allergic diseases and asthma. Surprisingly, the authors found that cytokine production in T cells from atopic individuals is not what the T-helper 1 and T-helper 2 (Th1/Th2) theory predicts. The Th1/Th2 theory has dominated immunological thinking about allergic and asthmatic diseases for the past decade, and maintains that Th1 cells, which produce interferon γ and interleukin 2, are responsible for cell-mediated immune

responses against intracellular pathogens. Th2 cells, which produce interleukin 4 and interleukin 13, direct immune responses against intestinal helminths.¹ Th1 cells also cause autoimmune diseases, while Th2 cells cause allergic diseases and asthma. Because Th1 and Th2 cells cross-regulate each other, the Th1/Th2 theory predicts allergic diseases develop when there are too many Th2 cells and not enough Th1 cells. When first proposed in 1986,² the Th1/Th2 theory revolutionised immunological thinking because it

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provided a clear mechanism that explained immune deviation (split tolerance), or how humoral immunity occurs without cell-mediated immunity, and vice versa.² The Th1/Th2 theory also showed the immune system's flexibility, and that a T cell's function was not predetermined in the thymus, but was established during immune stimulation (eg, by the cytokine microenvironment). The idea also suggested that predominant Th2 responses might be corrected by adding Th1 cells.³

Over the past several years, the Th1/Th2 theory has been challenged for two reasons: Th1 and Th2 cells are both pro-inflammatory; and Th1 cells do not always cross-regulate Th2 cells, but instead might exacerbate Th2-mediated diseases.^{4,5} Heaton and colleagues now show another problem with the Th1/Th2 theory: people with atopic disease are heterogeneous, and the Th1/Th2 dichotomy may not apply to everyone.

Heaton and colleagues studied several immunological variables in 175 children with well-characterised clinical features. The investigators stimulated peripheral blood cells from the children with antigen or allergen, examined the cytokines produced, and correlated the produced cytokines with specific disease patterns. The researchers confirmed that, in the general population, allergic diseases and asthma are associated with Th2 production, in particular interleukin 5, eosinophilia, and IgE production. Although this result accords with the Th1/Th2 notion, Heaton and colleagues found important exceptions. For example, production of interferon γ was associated with increased

immediate skin-test reactivity (and presumably led to worse allergies), and with airway hyper-reactivity. These associations show that Th1 responses could enhance the severity of allergic diseases and asthma, as trials in mice have predicted.^{4,5} Surprisingly, Heaton and colleagues found that people who had airway hyper-reactivity (but did not have allergies) produced higher concentrations of interleukin 10, suggesting that interleukin 10 might be a Th2 cytokine and enhance airways disease. However, interleukin 10 inhibited immediate skin-test reactions, which is consistent with the idea that interleukin 10 might also protect against allergic disease and asthma in some cases, as has been shown previously.⁶⁻⁸ Most importantly, Heaton found that cytokine patterns produced by lymphocytes were diverse among individuals. This diversity indicates that atopy is complex and influenced by genetic heterogeneity, and that environmental effects, such as infection or exposure to allergens, occur with varying intensities in different individuals. Heaton's findings suggest we rethink the Th1/Th2 notion and how it applies to human allergic diseases and asthma.

However, we should be cautious in interpreting the findings. Heaton and colleagues studied peripheral blood mononuclear cells. These cells might not represent immunological cells that are found in the target tissues in allergy and asthma, such as in the lung and nasal mucosa.⁹ In other words, the cell types that mediate and protect against allergy and asthma (eg, Th2-polarised cells and regulatory T cells^{10,11}) might be found primarily in mucosal tissue, and not in peripheral blood; therefore, studying blood cells could yield misleading results. Although Heaton used the best available technologies to study cytokine production in peripheral blood, if we examine effector and regulatory cell types from relevant target tissues, rather than from peripheral blood cells, we might form a more coherent and appropriate picture of immune regulation in human asthma and allergy, and develop a more unified theory of immune regulation. Until then, we should appreciate Heaton and colleagues' observations of cytokine production in atopic patients. They provide one of the most comprehensive views of the immunobiology of asthma and allergy in man.

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Measles surveillance: the importance of finding the tip of the iceberg

Chantal van Isterdael and colleagues recently published a study of completeness of reporting of cases of measles by general practitioners during an outbreak of measles in a community with low vaccination coverage in the Netherlands.¹ By surveying all families with children under 13 years of age served by a large general-practice group, they estimated a rate of measles attack of 10% (164 cases in 1654 children) according to parental diagnosis. The researchers noted that families sought health care for only 50 (30%) children with measles symptoms and that the perceived seriousness of illness, self-reported complications, and parental opinions that medical care should be sought for respiratory infections, were all significant factors in predicting which cases were brought to medical attention. The investigators also showed that of the 50 patients with measles seen or diagnosed in the clinic, only 15 (30%) were reported to the municipal health service. Combining these two proportions, van Isterdael and colleagues estimated that only 9% of all cases of measles in the population were reported by general practitioners to the municipal health service. We congratulate the authors for this addition to the sparse literature on sensitivity and completeness of measles surveillance (ie, the proportion of all cases of measles in the community that get reported).

Although many readers might be concerned that only 9% of patients with symptoms consistent with measles cases were reported to the public-health system, this result accords with previous studies. Harpaz recently published a review of studies of completeness of measles case reporting in the USA, in which he outlined the steps required for case detection and reporting: patient seeks health care, provider considers diagnosis of measles, and provider reports to public-health authorities.² Confirming the diagnosis is another critical step that might occur before or after the provider reports the case. Completion rates for each step can be assessed and the product of all of these rates is the overall reporting rate. The community-based reporting rates were 26% in Maryland in 1922–23,^{3,4} 10% in the USA in the decade before vaccine licensure in 1963,⁵ 7% in St

Louis in 1970–71,⁶ and 29% in Los Angeles in 1990–91.⁷ In the Los Angeles study, researchers noted an 80% rate of consultation, compared with 30% in the van Isterdael study. Other studies have assessed notification rates in patients who had been seen and diagnosed by health-care practitioners. Compared with the 30% notification by general practitioners in the van Isterdael study, 48% of patients seen and diagnosed with measles were reported to the health department in Los Angeles in 1990–91. In studies of people in hospital with measles, researchers found higher reporting rates: 58% in 1986 and 51% in 1989 in Los Angeles and 45% in New York in 1991.^{8,9} In general, the more severe the case of measles, the more likely it is to be reported, as was documented in the van Isterdael study.

Van Isterdael and colleagues rightly conclude that estimates of measles incidence, would be less than optimum on the basis of the less than 10% of measles cases diagnosed by parents that were reported by general practitioners in their study. Their study is an important reminder that passively reported measles cases are the tip of the iceberg of measles incidence. Most measles cases are unreported. However, even an insensitive passive surveillance system

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Measles virus (red envelope, blue nucleocapsid) budding off infected cell