# Treatment of periodontal disease in pregnancy

## Does not improve pregnancy outcomes, but should still be part of routine preventive care

RESEARCH, p 91

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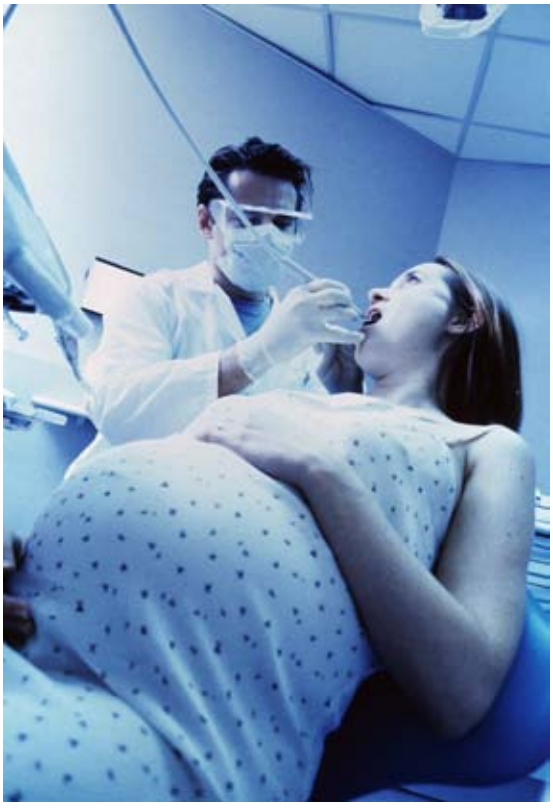
Epidemiological studies have shown that clinical and subclinical periodontal infections during pregnancy are associated with preterm birth. Infection is thought to result in the release of proinflammatory cytokines, which have downstream effects on other biological pathways and tissues. The association was first noted for bacterial vaginosis in the 1980s and 1990s, and randomised controlled trials were then performed to assess whether screening and treating the infection during pregnancy would improve pregnancy outcomes. Most of these trials found no benefit, and such screening is not currently recommended.[1] More recently, observational data have suggested that periodontal disease may also be linked to preterm birth and other adverse pregnancy outcomes.[2] Several large clinical trials have since been performed to assess whether pregnancy outcomes can be improved with treatment.

In the linked systematic review, Polyzos and colleagues assess whether treatment of periodontal disease with scaling and root planing during pregnancy is associated with a reduced rate of preterm birth.[3] The meta-analysis pooled the results of 11 randomised controlled trials, five of which were of high quality. Low quality studies tended to be much smaller than higher quality ones (with one study enrolling only 15 subjects per arm) and tended to overestimate the effect of treatment.[4] Given the large number of participants (2303 active treatment, 2290 placebo treatment) and lack of heterogeneity in the high quality studies, they deserve greater emphasis. The pooled results of the high quality studies do not a support a reduction in the risk of preterm birth (odds ratio 1.15, 95% confidence interval 0.95 to 1.40), low birth weight (1.07, 0.85 to 1.36), spontaneous abortions or stillbirths (0.79, CI 0.51 to 1.22), or overall adverse pregnancy outcome (1.09, 0.91 to 1.30) with treatment with scaling and root planing. The implications of this study are clear—scaling and root planing for the treatment of periodontal disease in pregnancy cannot be recommended.

Many questions about periodontal disease and pregnancy outcomes still warrant further research, however. Firstly, how should periodontal disease be defined? Interestingly, no real consensus exists, and even among high quality studies the definition varies. However, treatment was not effective in any of the studies regardless of the definition used. Secondly, does completely eliminating periodontal disease during pregnancy (most studies do not look at how effective the treatment was) improve pregnancy outcomes? A recent secondary analysis of one high quality randomised clinical trial supports this notion, but further study is needed.[5] Thirdly, would treatment at a different time—for example, before conception or very early in pregnancy—yield different results? Although an attractive theory, it may not be possible in everyday care because many women do not have interpregnancy care or even register for prenatal care early in pregnancy. Fourthly, would adjuvant treatment with antibiotics enhance the efficacy of scaling and root planing? So far, we have little evidence on adjuvant treatment during and outside of pregnancy. Fifthly, are specific oral bacterial pathogens often linked to preterm birth? Selective treatment of specific pathogens may be more effective. Lastly, is it possible, as shown in one randomised controlled trial, that treatment of periodontal disease can worsen some pregnancy outcomes?[6] This phenomenon was also seen in a randomised trial of screening and treating asymptomatic trichomoniasis in pregnancy.[7] Clearly, there are many avenues for future research on periodontal disease in pregnancy.



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Disappointingly, despites years of basic, clinical, and translational research, no robust data support the treatment of any infection to reduce preterm birth or improve pregnancy outcomes. This includes bacterial vaginosis, periodontal disease, trichomoniasis, and sexually transmitted diseases. It may be time to re-examine some basic assumptions about the cause of adverse pregnancy outcomes and explore new mechanisms and treatments.

What should clinicians tell their patients about periodontal disease, oral health, and pregnancy? The maintenance of oral health is an important part of routine preventive care, and should be encouraged during and outside of pregnancy. But it should be done as part of routine preventive care, rather than specifically to improve pregnancy outcomes.

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# Prevention of *Leishmania donovani* infection

## Vector control is key to the success of the global elimination strategy

**RESEARCH, p 92**

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Visceral leishmaniasis, the most severe form of leishmaniasis, is usually fatal in the absence of treatment. Together India, Nepal, and Bangladesh represent the biggest focus of visceral leishmaniasis in the world. Human to human transmission occurs through the bite of an infected sandfly, with no animal reservoir, a phenomenon known as anthroponotic transmission. Deadly epidemics occur periodically. The two main strategies to control the disease are case management and vector control. In the linked randomised controlled trial, Picado and colleagues assess the effect of the large scale distribution of longlasting insecticide treated nets on the incidence of visceral leishmaniasis in India and Nepal.[1]

Randomised controlled trials have shown that insecticide treated bed nets and curtains prevent anthroponotic cutaneous leishmaniasis in Afghanistan, Iran, and Syria.[2-4] Observational studies in Bangladesh and Nepal found a significantly reduced risk of visceral leishmaniasis in residents who used untreated nets nightly during the hot season.[5 6] However, an observational study in Bangladesh found that bed nets had no effect on asymptomatic leishmanial seroconversion.[7]

Picado and colleagues report the first large scale randomised controlled trial of the effectiveness of a comprehensive distribution programme of longlasting insecticide treated nets in an anthroponotic focus of visceral leishmaniasis. They found no significant difference in the risk of seroconversion (relative risk 0.90, 95% confidence interval 0.49 to 1.65) or clinical visceral leishmaniasis (0.99, 0.46 to 1.40) between groups who received treated nets and those who used usual preventive interventions (irregular indoor residual spraying and use of untreated nets) over 24 months. In addition, the distribution of treated nets did not reduce the annual incidence of visceral leishmaniasis below 18.8/10<thin>000, which is much higher than the target for elimination in the region (1/10 000).

Although studies in Nepal and Bangladesh showed sustained decreases in sandfly density of 89% and 60.5%, respectively, with the use of insecticide treated bed nets,[8 9] in Picado and colleagues' trial longlasting insecticide treated nets had a limited effect (25% decrease) on the indoor density of the vector *Phlebotomus argentipes*. In addition, the Kalanet pilot study found no decrease in indoor density of this vector with the use of treated nets.[10] This could explain the lack of effect on the incidence of visceral leishmaniasis. In addition, the authors suggest that the lack of effect may be explained by transmission occurring outdoors.

The limited impact of indoor residual spraying on the density of *P argentipes*, as reported in Picado and colleagues' study and elsewhere,[11] should be a signal to programme managers to check key factors in the process. These factors include the quality of DDT (dicophane), storage conditions, maintenance of equipment, staff performance, bioavailability of the insecticide in the treated nets, World Health Organization susceptibility test results (to check that the treated nets are actually killing sandflies), the level of acceptability by communities, geographic coverage, and the impact on indoor sandfly density. Randomised trials that compare indoor residual spraying with longlasting insecticidal nets, and indoor residual spraying plus longlasting insecticidal bed nets are needed.

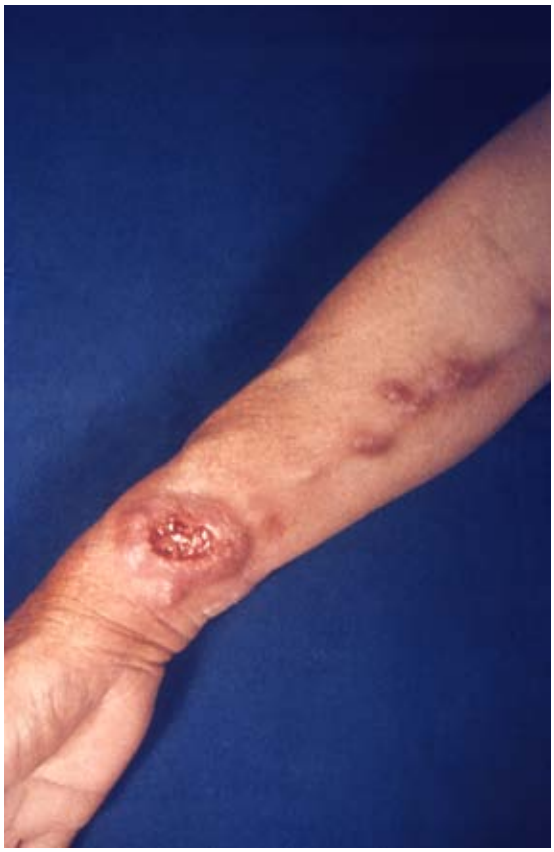
It is important that the negative results of this trial do not derail the current efforts to eliminate visceral leishmaniasis in South Asia. The factors responsible for the lack of efficacy of nets in the study should be identified and analysed to guide vector control strategies and policies.

The results were obtained from two areas: three districts in Nepal and one district in India. They could theoretically be extrapolated to Bangladesh, where the epidemiology is similar (anthroponotic transmission, same vector, and same *Leishmania* species). However, a complementary trial in Bangladesh would be advisable because the experience in vector control is limited, the susceptibility of *P argentipes* is unknown, the incidence of post-kala-azar dermal leishmaniasis is high, and yearly floods may have an effect on breeding sites.

The results cannot be generalised to countries in east Africa where visceral leishmaniasis is endemic because the epidemiology is very different in those countries (different vectors—*P orientalis* and *P martini*; presence of *L donovani* and *L infantum*; transmission is mainly anthroponotic but areas of zoonotic transmission also exist; incidence of post-kala-azar dermal leishmaniasis is high; and, in Ethiopia, coinfection with leishmania and HIV is common.)

Field research is needed in India, Nepal, and Bangladesh to answer several important questions and to optimise vector control: What is the current susceptibility of *P argentipes* to insecticides (DDT and pyrethroids) in each country? Does *P argentipes* bite indoors (endophagic) or outdoors (exophagic), and does it rest inside (endophilic) or outside (exophilic). Existing data support the view that *P argentipes* is endophilic and endophagic,[12] but work is needed to test whether it might also be exophagic. What are its host feeding preferences, resting and breeding sites, and flight range? What reduction in the density of *P argentipes* is needed to decrease the incidence of visceral leishmaniasis significantly? Are cattle protective or a risk factor? Because cattle are never infected by leishmaniasis, the spread of infection may be reduced by sandflies biting cows instead of humans. On the other hand, cattle dung provides a good breeding site for the maturation of sandfly eggs. What environmental measures can help reduce transmission? People with post-kala-azar dermal leishmaniasis and coinfection with HIV are thought to be highly infectious, so should they be priority targets for the use of treated bed nets?

India, Nepal, and Bangladesh have embarked on a programme to eliminate visceral leishmaniasis in 2005. Vector control is a key element of the global strategy to eliminate this disease. If it does not receive the level of attention it deserves, the current elimination programme will fail and a unique opportunity will have been lost.



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# Is estimating lifetime cardiovascular risk useful?

## No, but forecasting short term risk throughout life is

RESEARCH, p 93

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One of the exercises we set our medical students when introducing clinical epidemiology is to present the risk profile of a middle aged man and ask them to estimate his risk of death. Eventually someone works out the answer—100%. Death is inevitable, it is when and how the patient dies that are important. So does the QRISK lifetime cardiovascular risk model described in the linked study by Hippisley-Cox and colleagues have any more clinical relevance than the lifetime risk of death?[1]

The QRISK lifetime cardiovascular risk model was derived from the QResearch database, an ongoing extract of clinical and administrative data from electronic general practice records in England and Wales, dating back to 1994. The database has generated the world's largest cardiovascular risk prediction cohort study, which now includes more than three million people aged 30-84 years. The linked study reports that one in two British women have an estimated lifetime cardiovascular risk of over 30% and one in 10 have a risk of 50% or more. For men the equivalent risks are 40% and almost 65%.

Would this information help clinicians tailor treatment any differently for patients at the 50th centile of risk compared with those at the 90th centile? Both risks are substantial because cardiovascular disease is the main cause of morbidity and mortality in Britain. Therefore, the whole population, whatever their individual predicted lifetime risk, should be informed of the high "national" lifetime risk of cardiovascular disease and receive general advice about how to reduce it. Indeed, the major value of lifetime risk calculations is to inform health policy and planning rather than personalised healthcare.

From a clinical perspective, another problem with a personal lifetime cardiovascular risk estimate is how to determine the optimum value to aim for. Counterintuitively, the ideal is probably 100%, with the first cardiovascular event being sudden death while sleeping, some time after making it to 100 years of age. Furthermore, some groups at high risk of premature death, like smokers, may have a lower lifetime risk of cardiovascular disease than non-smokers because cancer kills them first.[2]

So what information about cardiovascular risk would best inform clinical decisions? The clinician's main role here is to identify those patients at highest risk who will benefit most from specific individualised interventions and to determine when these interventions should be started. We now have a wide range of relatively cheap safe drugs that can more than halve the risk of a cardiovascular event within about five years.[3] However, the absolute benefits of these drugs, and their cost effectiveness, are directly proportional to the patient's risk of having a cardiovascular event during the same period.[4] The QRISK research group is already a world leader in developing the short term cardiovascular risk prediction tools that clinicians need to identify these high risk patients (www.qintervention.org/index.php).[5] So why do clinicians continue to ask for information about their patients' longer term risk?

The main reason is the challenge of managing younger patients with multiple cardiovascular risk factors, like the 40 year old male "ticking time bomb" who smokes, is overweight, has a blood pressure of 150/90 mm Hg, and a total cholesterol to high density lipoprotein cholesterol ratio of six, yet has a 10 year cardiovascular risk, according to QRISK's short term risk calculator, of only 5% (www.qintervention.org/index.php). The 10 year risk is unhelpful for informing this patient what his future may hold, because short term cardiovascular risk is strongly age dependent and does not capture the importance of younger patients' longer term risk. However, does this patient's predicted lifetime cardiovascular risk—the risk of having a cardiovascular event if he lives to 95—provide any more useful information?

His lifetime cardiovascular risk, based on a new QRISK lifetime risk calculator, is about 50%, and if he stops smoking, loses 10 kg, drops his systolic blood pressure by 10 mm Hg and his lipid ratio by one unit, this risk will fall to 40%. Unfortunately, this adds little to the predicted 10 year risk. Of far more relevance is the graphic display (www.qrisk.org/lifetime/index.php), included as part of the calculator's output (examples for two other patients are shown in boxes 1 and 2 in the linked paper). The graphs present a continuous prediction of patients' cumulative cardiovascular risk throughout their lifetime, based on both current risk profiles and if their risk profiles improve. The most important risk related factor—time—is incorporated into the graph, and it is simple to read off the predicted risk for any time period from a few years to a lifetime.

The new QRISK cumulative cardiovascular risk graph is similar to the heart age forecast tool (www.knowyournumbers.co.nz/heart-age-forecast.aspx),[6] although the latter includes an additional metric—the patient's estimated "heart age"—to help with risk communication. Cardiovascular risk forecast calculators incorporate both short and longer term risk in one simple display and so have important advantages over separate 10 year and lifetime cardiovascular risk calculators.

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# Treating inflammatory arthritis early

## Sustained remission depends on rapid diagnosis and intensive treatment

**CLINICAL REVIEW, p 95**

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Inflammatory arthritis is a major healthcare problem. It spans rheumatoid arthritis, seronegative arthritis, and childhood arthritis. Three linked articles outline its clinical and personal effects.[1-3] Two clinical reviews challenge traditional management approaches, and a patient's personal testimony highlights the limitations of traditional care. The past decade saw major improvements in managing inflammatory arthritis, captured in guidelines from the National Institute for Health and Clinical Excellence (NICE) and other European and North American groups.[4-7] Despite such advances, far more is needed to overcome the long term effects of inflammatory arthritis on patients and carers.

Rapid diagnosis and treatment are crucial.[1 4-7] Patients need early effective treatment with disease modifying antirheumatic drugs (DMARDs). Traditional, cautious, symptom relieving approaches have become untenable for early inflammatory arthritis. A brief "window of opportunity" exists when effective treatment radically improves long term outcomes.[1 4-7] Delaying the start of DMARDs by more than three months since onset of symptoms perpetuates joint inflammation. The consequences are substantial joint damage and disability and lost independence.[1 4-7] It is therefore important to identify and treat inflammatory arthritis at the earliest opportunity. Intensive early suppressive treatment should target remission and prevent joint damage.[1 4-7]

Currently, many patients with inflammatory arthritis present late. The National Audit Office surveyed practice in the United Kingdom in 2009. They found that most people with symptoms suggesting inflammatory arthritis wait for three months before consulting their general practitioner. A fifth wait for more than 12 months.[8] One priority is to raise public awareness of arthritis so that people seek prompt medical advice. The UK Rheumatology Futures Group, Arthritis Research UK, and general practitioners are promoting public knowledge through the "S factor" campaign—stiffness, swelling, and the squeezing of joints causing pain mean that medical help is needed.

Diagnosing early inflammatory arthritis challenges both general practitioners and specialists. Low levels of clinical suspicion are essential because no ideal diagnostic tests exist. Patients often have normal inflammatory markers when first seen. The National Audit Office reported that people with inflammatory arthritis visit their general practitioner more than four times before specialist referral.[8] A second priority is for healthcare commissioners, the Department of Health, and the royal colleges to ensure that general practitioners receive ongoing training to help them recognise early inflammatory arthritis. Clinicians seeing patients with potential inflammatory arthritis should have low diagnostic thresholds and refer patients urgently. If squeezing across the metacarpophalangeal or metatarsophalangeal joints causes pain, this should trigger concern. Clinical features are more important than tests. New criteria will make diagnosis less demanding.[9] Referral must not be delayed until test results are available.[1 4] General practitioners need rapid access to expert multidisciplinary teams working together in specialist centres who can follow up patients regularly to achieve rapid disease control.[1 4]

Early, intensive DMARD treatment with regular follow-up—a key NICE guideline recommendation—has substantial implications for resources.[4] However, by reducing morbidity and disability it will eventually save money. The National Audit Office calculated that rapid specialist access with early intensive treatment and follow-up would increase NHS costs by £11m (€13m; $17m) over five years. Thereafter it would be cost neutral. It would also reduce sick leave and limit unemployment, thereby achieving £31m in gained productivity for the UK economy.[8] Long term extension studies of randomised controlled trials show that early DMARDs enable more patients to remain employed.[10] Evidence from a systematic review showed that poorly controlled inflammatory arthritis has large societal costs.[11] We cannot afford suboptimal treatment for inflammatory arthritis.

CHASSENET/SPL

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A personal view from the parent of a young patient with rheumatoid arthritis is available online (*BMJ* 2011;342:c7450)

When DMARDs fail to control rheumatoid arthritis patients need biological treatments, such as tumour necrosis factor inhibitors. These are both highly effective and expensive (£8000-£10 000/patient/year). Treating all patients with biologicals is clearly unaffordable. However, undertreating inflammatory arthritis also has high personal and societal costs. When biologicals were first introduced, large numbers of patients had very active disease. Times have now changed and clinical remission is achievable. In most of western Europe and North America biologicals can be used when patients have failed DMARDs and have ongoing active disease. Existing NICE guidelines mean that in the UK many patients with active arthritis do not fulfil the eligibility criteria to receive evidence based biological treatment. The UK should adopt more universal Western criteria.[12]

Limiting access to effective treatments is never defensible, whether based on UK postcodes or European country. The final priority is to make remission a UK quality standard when treating inflammatory arthritis. The challenge for rheumatologists, regulators, and commissioners is to ensure that patients get the treatment they need to achieve long term remission in ways that are deliverable and affordable.

Modern intensive treatments enable many patients with inflammatory arthritis to achieve sustained remission. Ailsa Bosworth's personal story, which shows what can be achieved in the face of personal adversity, highlights the limitations of treating arthritis too little and too late.[3] General practitioners, specialists, and healthcare commissioners must work together to ensure that patients receive both early and effective care.

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# Wakefield's article linking MMR vaccine and autism was fraudulent

## Clear evidence of falsification of data should now close the door on this damaging vaccine scare

**FEATURE, p 77**

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"Science is at once the most questioning and . . . sceptical of activities and also the most trusting," said Arnold Relman, former editor of the *New England Journal of Medicine*, in 1989. "It is intensely sceptical about the possibility of error, but totally trusting about the possibility of fraud."[1] Never has this been truer than of the 1998 *Lancet* paper that implied a link between the measles, mumps, and rubella (MMR) vaccine and a "new syndrome" of autism and bowel disease.

Authored by Andrew Wakefield and 12 others, the paper's scientific limitations were clear when it appeared in 1998.[2 3] As the ensuing vaccine scare took off, critics quickly pointed out that the paper was a small case series with no controls, linked three common conditions, and relied on parental recall and beliefs.[4] Over the following decade, epidemiological studies consistently found no evidence of a link between the MMR vaccine and autism.[5-8] By the time the paper was finally retracted 12 years later,[9] after forensic dissection at the General Medical Council's (GMC) longest ever fitness to practise hearing,[10] few people could deny that it was fatally flawed both scientifically and ethically. But it has taken the diligent scepticism of one man, standing outside medicine and science, to show that the paper was in fact an elaborate fraud.

In a series of articles starting this week, and seven years after first looking into the MMR scare, journalist Brian Deer now shows the extent of Wakefield's fraud and how it was perpetrated. Drawing on interviews, documents, and data

made public at the GMC hearings, Deer shows how Wakefield altered numerous facts about the patients' medical histories in order to support his claim to have identified a new syndrome; how his institution, the Royal Free Hospital and Medical School in London, supported him as he sought to exploit the ensuing MMR scare for financial gain; and how key players failed to investigate thoroughly in the public interest when Deer first raised his concerns.[11]

Deer published his first investigation into Wakefield's paper in 2004.[12] This uncovered the possibility of research fraud, unethical treatment of children, and Wakefield's conflict of interest through his involvement with a lawsuit against manufacturers of the MMR vaccine. Building on these findings, the GMC launched its own proceedings that focused on whether the research was ethical. But while the disciplinary panel was examining the children's medical records in public, Deer compared them with what was published in the *Lancet*. His focus was now on whether the research was true.

The Office of Research Integrity in the United States defines fraud as fabrication, falsification, or plagiarism.[13] Deer unearthed clear evidence of falsification. He found that not one of the 12 cases reported in the 1998 *Lancet* paper was free of misrepresentation or undisclosed alteration, and that in no single case could the medical records be fully reconciled with the descriptions, diagnoses, or histories published in the journal.

Who perpetrated this fraud? There is no doubt that it was Wakefield. Is it possible that he was wrong, but not dishonest: that he was so incompetent that he was unable to fairly describe the project, or to report even one of the 12 children's cases accurately? No. A great deal of thought and effort must have gone into drafting the paper to achieve the results he wanted: the discrepancies all led in one direction; misreporting was gross. Moreover, although the scale of the GMC's 217 day hearing precluded additional charges focused directly on the fraud, the panel found him guilty of dishonesty concerning the study's admissions criteria, its funding by the Legal Aid Board, and his statements about it afterwards.[14]

Furthermore, Wakefield has been given ample opportunity either to replicate the paper's findings, or to say he was mistaken. He has declined to do either. He refused to join 10 of his coauthors in retracting the paper's interpretation in 2004,[15] and has repeatedly denied doing anything wrong at all. Instead, although now disgraced and stripped of his clinical and academic credentials, he continues to push his views.[16]

Meanwhile the damage to public health continues, fuelled by unbalanced media reporting and an ineffective response from government, researchers, journals, and the medical profession.[17 18] Although vaccination rates in the United Kingdom have recovered slightly from their 80% low in 2003-4,[19] they are still below the 95% level recommended by the World Health Organization to ensure herd immunity. In 2008, for the first time in 14 years, measles was declared endemic in England and Wales.[20] Hundreds of thousands of children in the UK are currently unprotected as a result of the scare, and the battle to restore parents' trust in the vaccine is ongoing.

Any effect of the scare on the incidence of mumps


TEK IMAGE/SPL

remains in question. In epidemics in the UK, the US, and the Netherlands, peak prevalence was in 18-24 year olds, of whom 70-88% had been immunised with at least one dose of the MMR vaccine.[21 22] Any consequence of a fall in uptake after 1998 may not become apparent until the cohorts of children affected reach adolescence. One clue comes from an outbreak in a school in Essen, Germany, attended by children whose parents were opposed to vaccinations. Of the 71 children infected with mumps, 68 had not been immunised.[23]

But perhaps as important as the scare's effect on infectious disease is the energy, emotion, and money that have been diverted away from efforts to understand the real causes of autism and how to help children and families who live with it.[24]

There are hard lessons for many in this highly damaging saga. Firstly, for the coauthors. The GMC panel was clear that it was Wakefield alone who wrote the final version of the paper. His coauthors seem to have been unaware of what he was doing under the cover of their names and reputations. As the GMC panel heard, they did not even know which child was which in the paper's patient anonymised text and tables. However, this does not absolve them. Although only two (John Walker-Smith and Simon Murch) were charged by the GMC, and only one, the paper's senior author Walker-Smith, was found guilty of misconduct, they all failed in their duties as authors. The satisfaction of adding to one's CV must never detract from the responsibility to ensure that one has been neither party to nor duped by a fraud. This means that coauthors will have to check the source data of studies more thoroughly than many do at present—or alternatively describe in a contributor's statement precisely which bits of the source data they take responsibility for.

Secondly, research ethics committees should not only scrutinise proposals but have systems to check that what is done is what was permitted (with an audit trail for any changes) and work to a governance procedure that can impose sanctions where an eventual publication proves this was not the case. Finally, there are lessons for the Royal Free Hospital, the *Lancet*, and the wider scientific commu-

nity. These will be considered in forthcoming articles.

What of Wakefield's other publications? In light of this new information their veracity must be questioned. Past experience tells us that research misconduct is rarely isolated behaviour.[25] Over the years, the *BMJ* and its sister journals *Gut* and *Archives of Disease in Childhood* have published a number of articles, including letters and abstracts, by Wakefield and colleagues. We have written to the vice provost of UCL, John Tooke, who now has responsibility for Wakefield's former institution, to ask for an investigation into all of his work to decide whether any more papers should be retracted.

The *Lancet* paper has of course been retracted, but for far narrower misconduct than is now apparent. The retraction statement cites the GMC's findings that the patients were not consecutively referred and the study did not have ethical approval, leaving the door open for those who want to continue to believe that the science, flawed though it always was, still stands. We hope that declaring the paper a fraud will close that door for good.

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