

1997, according to DiMatteo, and she expects another doubling again since 1997. While only comprising about 2% of the land used for agriculture, organic farming accounts for large areas in certain locations, such as Vermont, where 24% of all vegetable production is organic. In Europe, this figure overall is around 3.4%. The OTA maintains that the demand for organically grown crops is on the rise; so too is public disdain for bioengineered crops. But it is only a niche market, and organic, environmentally friendly farming certainly comes with a higher price tag for the consumer.

A middle ground between IPM and organic could be 'biointensive or ecology-based IPM', which aims to decrease inputs of fuel, machinery and synthetic chemicals, according to ATTRA. Biointensive IPM takes a 'systems' approach and, as such, resembles the original concept of IPM that emphasises restoring and enhancing the natural balances in the ecosystem, not just the elimination of pests. For this approach, ATTRA warns against the use of synthetic pesticides, noting that they often cause resistance similar to that seen with the overuse of antibiotics and can actually lead to a resurgence of pests by killing off natural

beneficial organisms. It advises creating habitats to enhance the reproduction of beneficial pests, so-called farmscaping, and the use of less toxic chemical pesticides such as soaps, oils, boric acid, sugar esters and pesticides derived from naturally occurring compounds such as pyrethrum, neem, rotenone and *Bacillus thuringiensis*. Perhaps this form of IPM will appease all parties and be the farming of the future.

Vicki Brower

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Injection of confidence

The recent controversy in the UK has led to falling MMR vaccination rates

The media love a whistleblower. Particularly with the current mistrust of science, one lone voice pitted against the majority of scientific opinion is guaranteed to grab the public's attention. And this is exactly what has been happening in the UK since a study in the April 2002 issue of *Molecular Pathology* (pre-published online in February) found that 75 out of 91 children with autism had traces of the measles virus in their gut compared to only 5 out of 70 healthy children. A striking statistic indeed, but the senior author of this paper has used this fact to promote concerns that the combined measles, mumps and rubella (MMR) vaccine could be the trigger for the developmental regression in these children. Predictably, MMR uptake rates in the UK are falling, and some inner cities, particularly London, are witnessing their first measles outbreak for a decade.

The World Health Organization (WHO) aims to eradicate measles by 2007, but, in order to do so, it recommends that more than 95% of the population are vaccinated against the disease. Globally, the current average is 80% coverage; some countries, such as Finland, better than with a 99% uptake rate of the MMR vaccine, whereas France has 85%, Germany a meagre 70% and, with the

current controversy, the UK's average rates are now falling from ~92 to 88% and are even down to 65% in some areas. This is in the face of a mounting body of



scientific evidence that this combined vaccine is actually one of the safest ever produced. Similar battles revolving around public confidence in vaccines have drifted in and out of the headlines in the past, but this trend in falling immunisation

rates needs to be reversed before unnecessary deaths occur or the concern spreads beyond the UK or even to other vaccines. Hans Wilhelm Doerr, the Director of the Institute of Medical Virology in Frankfurt, Germany, commented: 'It seems to be the fate of every successful vaccination programme, that—if the infectious disease could be eradicated—the fear of adverse effects rises.'

Advances in modern medicine have been such that 10 diseases are now preventable by vaccination, requiring a total of 18 injections—some combined into a single jab—and three oral administrations by the age of two. Table I shows the immunisation schedule for the UK; although this is broadly similar for the US and the rest of Europe, each country has its own recommendations. Ironically, the success of these vaccines has led to a virtual elimination of these diseases in the developed world, and so parents are now questioning the need for these injections. But these infectious agents are all still very real threats in more developing countries—for example, 890 000 children die as a result of measles worldwide each year—and can easily be reintroduced through international travel and, potentially, climate change. Therefore, 'herd immunity' is required, where a sufficiently high

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Table I. The British childhood immunisation schedule

	DPT-Hib	OPV	MenC	MMR	DT	BCG
2 months	√	√	√			
3 months	√	√	√			
4 months	√	√	√			
12–15 months				√		
3–5 years				√	√	
10–14 years						√

DPT-Hib, diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b; OPV, oral poliomyelitis vaccine; MenC, meningococcal serogroup C conjugate vaccine; MMR, measles, mumps, rubella; DT, diphtheria, tetanus; BCG, Bacillus Calmette-Guerin for tuberculosis.

proportion of the population is immune such that the infectious agent cannot be transmitted efficiently. If this drops below a critical level—around 95%, but estimates vary—the population is vulnerable, as was borne out after the collapse of the

with the rest of the hospital, Wakefield has continued to be outspoken against the triple vaccine, which has added to the media frenzy with his pronouncements around the time of the release of his recent study published in *Molecular*

we have major problems that need to be addressed, and they're not addressed by burying our heads in the sand and pretending the problem of questionable vaccines will go away.'

The vast majority of scientists and specially convened committees are coming out overwhelmingly in favour of the trivalent vaccine and categorically state that the conclusions Wakefield draws are flawed and inconclusive. They instead point to numerous studies carried out in the UK, the US, Finland and Sweden that have shown that there is no causal link between the measles component of the vaccine, intestinal abnormalities and autism. These are generally epidemiological in nature, and it has been extensively shown that the sharp rise in autism cases reported in the last few years does not coincide with the introduction of the MMR vaccine. The converse has also been shown to be true, in that the incidence of developmental regression accompanied by bowel disorders does not change, irrespective of whether an afflicted child has been given the MMR vaccine. In particular, a Finnish study followed 1.8 million children for 14 years and found no serious side effects of the vaccine, although critics point to the fact that autism was not a specific criteria looked for in these children. Official studies aside, it is clear that 500 million doses of the vaccine throughout 90 countries have been administered largely without problem for the last 30 years. But there is ample evidence that administering the single vaccines separately as advocated by the MMR opponents, and now apparently by 75% of British parents, will increase the incidence of these diseases. It would entail more trips to the

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Soviet Union: vaccines were in short supply in the newly independent states, and the number of polio, measles and, particularly, diphtheria cases rose sharply to epidemic levels. A serious outbreak of measles in Dublin, Ireland, in 1999–2000, caused by parents shunning the MMR injection, left two children dead and many more permanently damaged. For developed countries where vaccines are widely available, immunisation therefore becomes a 'social duty', but it is one which needs to appear more advantageous to the currently sceptical public.

A possible link between the MMR combined vaccine and developmental regression was first raised in 1998 in a study of 12 children published in the *Lancet*, which claimed that the vaccine triggered a 'new variant' of autism, typically accompanied by bowel disorders. The first-name author of this paper, Andrew Wakefield, was a reader in experimental gastroenterology at the Royal Free Hospital, London, and his contact there with distraught parents of autistic children, who associated the onset of symptoms with the first MMR injection, led him to investigate the vaccine further. Despite leaving the Royal Free in November 2001 by 'mutual agreement' because his research strategy was no longer in line

Pathology. Even though the other authors and the journal's editors were at pains to point out in the article and the accompanying press release that no link with MMR had been proven, or even looked for in this study, Wakefield continues to publicly promote his own view that there is a link between the vaccine and autism. Until more thorough investigations are carried out, he advocates the introduction of single vaccines, claiming that the simultaneous administration of three live viruses is unnatural and overloads the immune system, leading to a persistent measles infection in the gut. Gastrointestinal symptoms

'Herd immunity' is required, where a sufficiently high proportion of the population is immune such that the infectious agent cannot be transmitted efficiently

are often recorded during such an infection, and there is evidence that developmental disorders can be triggered by disturbances in the brain–gut axis. Speaking to the *British Medical Journal*, Wakefield said: 'It has been very difficult for my colleagues to come to terms [with the fact] that there may be a genuine problem with inoculations, something that is supposed to be one of the great medical achievements of the 20th Century. Unfortunately

doctors, more needles and unnecessary gaps between injections that leave a child unprotected. In Japan, the only country to offer the monovalent measles and rubella vaccines, there were 79 deaths from measles between 1992 and 1997. Moreover, it is currently pure conjecture that the problem lies with the interaction of the trivalent vaccine components, and it has not been established that single vaccines would even be a safer option.

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This current publicity is fanning the flames of parents' existing concerns that the number of injections required by children places an unnecessary demand on their inadequately developed immune systems. In response to the MMR allegations, a study published in *Pediatrics* in January 2002 estimated how many antigens a child's immune system can theoretically respond to, and it found quite the reverse to be true. The highly developed immune system of the neonate must have the ability to cope with emerging from the relatively sterile *in utero* environment into the bacteria-clogged outside world and so has an enormous capacity to immediately respond to a wide variety of antigens—a conservative estimate would be 10¹¹. The MMR vaccine currently contains 24. Added to which, the high purity of today's vaccines means that children are actually being exposed to fewer antigens than in previous years, particularly with the introduction of the acellular rather than the whole cell pertussis vaccine and the eradication of smallpox.

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This has effectively reduced the number of antigens to which a child is exposed by vaccination from around 3000 in 1980 to 125 today. Moreover, vaccines are thought to have a heterologous effect and boost the overall efficiency of the immune response to any infection.

In western communities, failure to fully vaccinate children is largely the result of conscious parental decision. People are unaware of the risks that these diseases pose, and potential side effects, however tenuous, take on a disproportionate importance. In particular, the infections preventable by the MMR vaccine are not viewed as killers but rather as benign inconveniences. Given the presupposed choice between putting their child at risk of a life-long debilitating condition and a week in bed with a rash, it is hardly surprising that parents are increasingly opting for the latter. But, before 1974, when the Expanded Programme on Immunisation was established, 8 million children died of measles worldwide every year and many survivors were left with permanent disabilities. Now that the disease has all but disappeared in many of the developed countries, the apparent

benefit of immunisation for any given individual is decreasing while the perception of risk is increasing. 'To estimate risk you need both sides of the equation and

Wakefield has continued to publicly promote his own view that the vaccine is not safe

it's much easier if you base this on personal experience,' said David Elliman, consultant in child health at St George's Hospital, London. 'At the moment, these [diseases] are theoretical risks which have nowhere near the same impact. Measles is just something on some old newsreel.' In contrast, parents are currently being exposed to the effects of autism via the media, and this is what leaves a lasting impression.

Although MMR vaccination rates are falling in the UK, this does not seem to be reflected elsewhere in the world. Neal Halsey, director of the Institute for Vaccine Safety at Johns Hopkins University, Baltimore, MD, commented about the

US: 'We have maintained very high coverage rates with MMR. I believe the latest figures are around 95%.' In Germany, the MMR uptake rate is currently around 70%, way below the WHO target for the eradication of measles. Correspondingly, this country has around 7000–10 000 cases of measles per year, although as a non-reportable disease this could be an underestimate. This is not specifically due to the current concerns about MMR but more a general mistrust of vaccines, in addition to the widespread belief that to have the natural infection is preferable to

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an 'unnatural' vaccination. Homeopathic sympathies are common, and outbreaks can often be traced to schools with particularly anthroposophic parents. Ironically, as Doerr pointed out: 'Unfortunately, it has been forgotten that Samuel Hahnemann, the founder of homeopathic medicine, had been inspired by Jenner, the founder of modern vaccination.'

In the quest for a good story, journalists invariably give equal weight to both sides, elevating unproven concerns to the same level as published, scientific data. And as Elliman pointed out: 'It's sad that a lot of people base their information on what they read in the popular press. The medical correspondent will often write a very good article and then the editor goes and puts a scary headline on it and a picture of someone with autism. And that's the message that people go away with.' The problem is compounded by the fact that most of the data supporting the combined MMR vaccine have been obtained by its manufacturers, which counts as worthless in many people's eyes. 'You show me someone who doesn't have a vested interest in research,' Elliman said. 'We should ask people if they'd be happier if the drug companies or the government fund it as a lot of people would put the two into the same camp. Charities just cannot afford this type of study; they are just too big.'

There is the real danger that this debate will harm public perception of vaccines in general, particularly if the fear of overloading a child's immune system takes hold. As we learn more about how to control diseases, the number of injections recommended for infants will only increase. Manufacturers, therefore, are keen to develop combination vaccines, which should prove popular by reducing the number of needles and trips to the doctor. Indeed, GlaxoSmithKline (Uxbridge, UK) is currently obtaining approval for its MMRV vaccine (MMR plus varicella) to simultaneously immunise against chickenpox. Hexavac (Aventis Pasteur, Lyon, France) and Infanrix Hexa (GlaxoSmithKline) both protect against diphtheria, tetanus, pertussis, hepatitis B, polio and *Haemophilus influenzae* type b

(DtaP-HBV-IPV-Hib). They are licensed throughout the EU, and this is also 'imminent' in the US according to Halsey. But that is probably about as far as we can push this concept at the moment. As Wolfgang Jilg from the University of Regensburg, Germany, and a prominent member of the German Association against Virus Diseases explains: 'The problem with these sort of vaccines is that combinations

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often behave in an unpredicted way. Some components show lower immunogenicity due to, for example, the pH or salt concentration in the combination. This is a problem for the manufacturer who has to perform large clinical trials to test and finally to demonstrate the good immunogenicity of every component of the vaccine.' Added to the potentially reduced immunogenicity of each component there are the problems of increased reactogenicity, shortened shelf-life and a complicated manufacturing procedure.

'These problems become bigger with every new component added to an already existing combination. I don't think we will have a 'Heptavac' with seven components in the near future,' he concluded.

Clearly, autism has a very complex aetiology involving a number of environmental and genetic factors that are not understood. It may still be that, in a minor subset of children with a genetic predisposition towards the disease, the measles virus in combination with other factors

acts as a trigger. But, unfortunately, public faith in a vaccine that is safe for the vast majority has been eroded, such that the number of measles cases is rising in the UK. Comparing this situation to previous pertussis vaccine scares, which led to unnecessary deaths from whooping cough in the 1970s, Elliman said: 'It's a very sad way of learning.'

Susan R. Owens

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