MMR vaccine and autism

Health professionals must enter the public arena if future debacles are to be prevented

PETER MACDIARMID/GETTY IMAGES

NEWS, p 281
OBSERVATIONS, pp 294, 295

Helen E Bedford senior lecturer in children's health, Centre for Paediatric Epidemiology and Biostatistics, UCL Institute of Child Health, London WC1 1EH
h.bedford@ich.ucl.ac.uk
David A C Elliman consultant in community child health, GOSH@ Haringey, Great Ormond Street Hospital for Children, London WC1N 3LU

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Two and a half years after beginning to hear evidence, the General Medical Council (GMC) has ruled that three researchers acted improperly in the conduct of their research into a proposed new syndrome of autistic enterocolitis.[1] It is 12 years since publication of the study in the *Lancet*, now retracted, which described the research to which the hearing relates.[2] Subsequent events have had a major impact on children's health.

The paper described 12 children with a pervasive developmental disorder and bowel disease, which, the authors suggested, was a new syndrome. In eight of the children, symptoms were reported to have started soon after receipt of the measles, mumps, and rubella (MMR) vaccine. In their conclusions, they stated, "we did not prove an association between measles, mumps and rubella vaccine and the syndrome described" and that more research was needed. However, at a press conference, one of the authors suggested that, rather than using the combined MMR vaccine, single vaccines for measles, mumps, and rubella should be given at yearly intervals. It was this statement, unsupported by the research, that sparked media interest. At the time, the supposed link between MMR and autism was shown to be without substance,[3] but it was predicted that this bad publicity could precipitate a vaccine safety scare that would result in reduced vaccine uptake and the return of measles. This has proved all too correct.

Because the media subsequently gave equal coverage to opposing views, parents understandably thought this meant that the scientific evidence for and against a link with autism was equally weighted.[4] The Department of Health launched an advertising campaign; produced materials for health professionals and parents with the message that "MMR immunisation is the safest way that parents can protect their children against measles, mumps, and rubella"[5]; and set up a dedicated website. However, the effects of earlier health controversies such as that relating to new variant Creutzfeldt-Jakob disease had already dented public trust in the government, and the MMR controversy had all the ingredients needed for a major health scare. The vaccine is offered to every young child, but previous high vaccination rates meant that few people remembered the seriousness of measles; autism on the other hand seemed to be prevalent.

Autism is a poorly understood condition that affects social and verbal communication, one of the most fundamental human characteristics. It is therefore not surprising that public concern increased, with parents describing the decision on whether to take up the MMR as difficult and stressful.[6] Parents were unsure whom to trust for impartial advice because of target payments to general practitioners[6]; many felt they could not get adequate answers to their questions and so turned to the internet for information, some of which was highly dubious.

Celebrities' public declarations of their negative personal opinions about the safety of MMR only added to the interest. Parents were bombarded by conflicting, often ill informed, opinion, so they understandably felt confused and anxious. Some rejected the MMR vaccine altogether, whereas others, often the more affluent,[7] sought out single vaccines on a private basis. Throughout this scare most parents continued to accept the MMR vaccine, although uptake fell from 92% in 1995-6 to 80% in 2003-4.[8] This was unlike the pertussis vaccine safety scare in 1970s, when parents had a choice of vaccines with or without the whole cell pertussis component, and uptake of the pertussis vaccine fell to 31%.[8] However, measles is so infectious that even a modest reduction in uptake affects disease rates. Cases of confirmed measles infection in all age groups have risen each year since 1998, with 1370 in 2008 and 1143 up to the end of November 2009. From 1995 to 2005, there were no deaths from measles, but since then there have been two in immunosuppressed teenagers.

Over time, an accumulating body of epidemiological and virological evidence failed to show any association of MMR with autism and bowel disease.[9] However, restoring public confidence after such a setback is challenging and takes time; it took 15 years for pertussis vaccine rates to recover. In the case of MMR, the reduction in uptake was not so pronounced, and parents' confidence in the vaccine recovered much quicker. This is reflected by improved uptake, with 86.5% of 2 year old children receiving the vaccine in early 2009.[10] At the same time the media have made a complete about turn, with most journalists now referring to the "discredited link."

Whatever ruling the GMC had made, it would have provided another platform for vocal anti-MMR campaigners to bring doubts about the safety of the vaccine to the forefront of the media once again, with a potential effect on a new set of parents. Although many children are not immunised because of difficulties accessing services, this can be tackled, at least in part, with accurate IT systems, reminders, and flexible immunisation services.[11]

The real challenge for professionals is restoring trust in parents who have decided that their children should not have the vaccine. Such parents include those of infants currently due to receive the vaccine, as well as those of the hundreds of thousands of children unprotected as a result of the scare in the early 2000s. For these parents, providing

bmj.com archive: MMR timeline

- Editorial. Is measles infection associated with Crohn's disease? (1998;316:166)
- Editorial. MMR vaccination and autism 1998 (1998;316:715-6)
- Editorial. Vaccination policies: individual rights v community health (1999;319:1448-9)
- Editorial. MMR vaccine: the continuing saga (2001;322:183-4)
- Editorial. Comparison of social distribution of immunisation with measles, mumps, and rubella vaccine, England, 1991-2001 (2003;326:854)
- Editorial. Has the UK government lost the battle over MMR? (2005;330:552-3)
- Research. Effects of a web based decision aid on parental attitudes to MMR vaccination: a before and after study (2006;332:146-9)
- Editorial. Improving uptake of MMR vaccine (2008;336:729-30)
- Research. Factors associated with uptake of measles, mumps, and rubella vaccine (MMR) and use of single antigen vaccines in a contemporary UK cohort: prospective cohort study (2008;336:754-7)
- MMR video: Wakefield and the MMR crisis (bmj.com/video/mmr.dtl)

clear and accurate information on the benefits and risks of the vaccine as well as the dangers of the diseases is only part of an effective approach. The nature of the communication with parents is crucial. They are more likely to respond to a professional who listens carefully and respectfully to their individual concerns, answers their questions honestly and openly, and acknowledges when information is lacking about a particular matter.[12] With this approach, and repeated opportunities to talk, parents who at first decline immunisation may be willing to reconsider.

Although responsibility for sparking this health scare must rest with the researcher who originally suggested a link, the media kept fuelling the flames. Unfortunately, at times, the response of health professionals was lukewarm, with few willing to engage in the public debate and many wavering in their support of the vaccine. If future debacles are to be prevented, professionals must enter the public arena, even though there can be unpleasant ramifications (both the authors of this editorial have received hate mail and an American researcher has even received death threats). However uncomfortable this may be, we must be firm advocates of what is best for children's health, even if this seems to run contrary to "patient choice."

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Etanercept for psoriatic arthritis

Patients who do not respond to standard doses are unlikely to benefit from a higher one

RESEARCH, p 300

Dafna D Gladman professor of medicine, Toronto Western Hospital, 399 Bathurst Street, 1E-410B, Toronto, ON, Canada M5T 2S8
dafna.gladman@utoronto.ca

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In the linked randomised controlled trial Sterry and colleagues compared the effectiveness of two different etanercept regimens (50 mg once a week or twice a week) in treating the skin manifestations of psoriasis in people who also had psoriatic arthritis over 12 weeks.[1]

Psoriatic arthritis is an inflammatory arthritis that affects about 30% of patients with psoriasis. Over the past few decades it has become clear that the disease is more common and more severe than previously thought. Studies in the 1940s indicated that the frequency of psoriatic arthritis in patients with psoriasis was 7%, but more recent studies suggest a frequency of 30%.[2] Psoriatic arthritis may cause joint destruction, disability, and reduced quality of life. Patients with the disease have more disability and a worse quality of life than those with psoriasis alone.[3] Although disease modifying antirheumatic drugs have been used to treat psoriatic arthritis, they have not altered the disease course or prevented the progression of joint damage.[4]

Since the advent of biological treatments, specifically anti-tumour necrosis factor (anti-TNF) agents, the management of psoriatic arthritis has improved. However, in general, the doses of these drugs have been extrapolated from those used in patients with rheumatoid arthritis, and we do not know whether they are appropriate for patients with psoriatic arthritis. This is particularly important because patients with psoriatic arthritis generally have a higher body mass index than those with rheumatoid arthritis, and with some of these agents higher doses are needed for patients with psoriatic arthritis.[5]

Etanercept was the first anti-TNF agent to be of benefit in patients with psoriatic arthritis.[6] The initial dose selected, 25 mg twice a week, was based on that used in patients with rheumatoid arthritis. Subsequently, the anti-TNF antibodies, infliximab and adalimumab, and more recently golimumab, have been shown to be effective in reducing both skin and joint inflammation, as well as dactylitis and enthesitis, in

Responses to various drugs in randomised clinical trials of psoriatic arthritis

		ACR 20%		ACR 50%		ACR 70%		PsARC		PASI75	
Drug tested	N	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Etanercept[6]	205	50	13	37	4	9	1	70	24	38	4
Infliximab[7]	200	54	16	41	4	27	2	70	32	60	1
Adalimumab[8]	315	58	14	36	4	20	1	62	26	59	1
Golimumab[9]	405	52	12	32	3.5	18	0.9	70	29	66	1.4
Etanercept (PRESTA)[1]	752	70	NA	52	NA	35	NAw	80	NA	70	NA

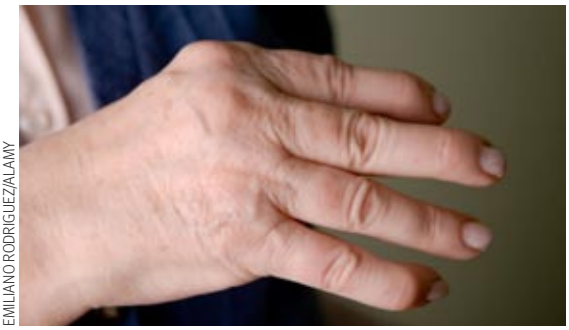
ACR=American College of Rheumatology; 20%, 50%, and 70% responses refer to achieving a 20%, 50%, or 70% reduction in tender and swollen joint counts and three of the following five measures: patient global assessment, physician global assessment, pain, disability, and an acute phase reactant. PsARC=psoriatic arthritis response criteria based on tender and swollen joint counts, patient global assessment, and physician global assessment. PASI75=75% improvement in the psoriasis area severity index; NA=not available.

psoriatic arthritis.[7-9] The dose of infliximab used in clinical trials is 5 mg/kg per infusion. In clinical trials for psoriasis, a loading dose of 80 mg of adalimumab was given, followed by 40 mg every other week. The perception among rheumatologists and dermatologists is that etanercept does not work as well as anti-TNF antibodies for skin symptoms, and that because of their higher body mass index, patients with psoriasis and psoriatic arthritis may need a higher dose of etanercept. Indeed, the dose of etanercept used in randomised clinical trials in psoriasis has been 50 mg twice a week for 12 weeks, followed by 50 mg weekly.[10] However, in psoriatic arthritis, only 50 mg once a week has been used.

In this context, Sterry and colleagues' trial is important.[1] The study showed that although 50 mg twice a week was more effective than 50 mg once a week for skin psoriasis, at least in terms of early response, the higher dose had no additional beneficial effect on the arthritis. The suggests that patients with psoriatic arthritis who do not respond adequately to a dose of 50 mg once a week are unlikely to benefit from a higher dose.

Some potential problems need to be considered. Although patients were required to have moderate to severe psoriasis, they needed to have only two tender and swollen joints. This is lower than the number of actively inflamed joints required for most other studies, which is at least three, and lower than the requirement for drug approval in most jurisdictions. However, the mean number of tender and swollen joints for the patients actually included in the study was high (mean of 19 tender and 12-13 swollen joints per patient). The number of tender and swollen joints recorded in these patients at baseline was similar to that recorded in other randomised controlled trials (25 tender, 14 swollen in the adalimumab and infliximab trials).

Although 92% of the patients were evaluated by a rheumatologist, the rest were assessed by independent assessors or dermatologists. The International Multicenter Psoriasis and Psoriatic Arthritis Reliability Trial (IMPART) study showed that dermatologists are not as good as rheumatologists in assessing swollen joints and digits with dactylitis.[11] Although this might not pose a major problem if patients were evaluated by the same assessor at each visit, it is still a concern.



EMILIANO RODRIGUEZ/ALAMY

Psoriatic arthritis in a 60 year old woman.

The lack of a standard treatment arm makes it difficult to interpret the results. It would have been useful to use methotrexate alone as the placebo arm with 50 mg and 100 mg per week of etanercept as the treatment arms. Moreover, to determine the best response to etanercept, the dose of 50 mg twice a week should have been continued beyond the 12 weeks.

How does etanercept compare with other anti-TNF agents? A review of all randomised controlled trials using anti-TNF agents shows that etanercept is as effective as the anti-TNF antibodies for the treatment of psoriatic arthritis (table). However, when it comes to assessing skin response, the PASI75 (psoriasis area and severity index) score is not as high in patients treated with etanercept as it is in patients treated with anti-TNF antibodies (table). Nonetheless, a meta-analysis of anti-TNF agents in psoriatic arthritis showed no significant differences in response among the various agents.[12]

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Measurement of postpartum blood loss

Better accuracy is only the first step towards improving outcomes

RESEARCH, p 301

Ndola Prata adjunct professor and research director, Bixby Center for Population, Health, and Sustainability, University of California, Berkeley, CA 94720, USA
Caitlin Gerdts doctoral student, Department of Epidemiology, University of California

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Delayed diagnosis and poor management of postpartum haemorrhage are associated with increased mortality and morbidity.[1-4] The challenge, particularly in developing countries, is to improve management—for example, by using prophylactic administration of uterotonics in deliveries. In the linked cluster randomised controlled trial, Zhang and colleagues assessed whether using a transparent plastic collector bag to measure postpartum blood loss after vaginal delivery reduced the incidence of severe postpartum haemorrhage.[1]

Clinicians continue to rely on visual assessment to determine the volume of postpartum blood loss. Studies have repeatedly shown visual estimates to be inaccurate (overestimating blood loss at low volumes and underestimating blood loss at high volumes).[5 6] Several technologies have been developed to help clinicians to measure postpartum blood loss more accurately, with the intention of improving outcomes after postpartum haemorrhage. These include direct collection of blood in pans, gravimetric measurement of sponges (weighed before and after use), spectrophotometric methods,[7] calibrated and non-calibrated drapes, and even enhanced teaching methods for visual estimation. Several studies in developed countries have reported that such interventions have improved the accuracy of measuring blood loss but that more accurate measurement has little effect on postpartum haemorrhage outcomes.[8-10]

Zhang and colleagues' trial, which was conducted in hospitals in 13 European countries, concluded that a more accurate assessment of blood loss is not, by itself, sufficient to affect rates of postpartum haemorrhage. The population included had a low incidence of postpartum haemorrhage of 1-2% and very low associated mortality. In this setting, clinicians' awareness of postpartum haemorrhage is high, and management—including prophylactic use of uterotonics in the third stage of labour—is standard.

In the developing world where most women deliver outside healthcare facilities and where trained clinicians are few (women are often accompanied by traditional birth attendants or family members) the public health importance of accurate measurement of blood loss may be different.

A recent randomised controlled trial of postpartum haemorrhage after home births with traditional birth attendants in Tanzania assessed the safety and effectiveness of a traditional blood loss measurement tool on the diagnosis and treatment of postpartum haemorrhage.[11] Here, traditional birth attendants place kangas (colourful, rectangular cotton garments of standard size, used by women in East Africa) under the woman's buttocks to absorb postpartum bleeding, and they use four blood soaked kangas as a threshold measure for postpartum haemorrhage, at which point women are referred to a health facility. A pilot study determined that two blood soaked kangas was slightly more than 500 ml of blood. Building on existing practice, traditional birth attendants in the trial were trained to diagnose postpartum haemorrhage after two kangas had been soaked through, and the study found that they could accurately diagnose postpartum haemorrhage and refer women to health facilities in a timely manner. Although this method does not provide a perfect measure of blood loss, by recalibrating the threshold for postpartum haemorrhage diagnosis from four blood soaked kangas to two, the timing of referral to a facility was greatly improved, reducing the risk of death from postpartum haemorrhage. Another trial conducted in a hospital setting in Karnataka, India, compared visual estimation of postpartum blood loss to estimation using a calibrated drape.[12] Visual estimation underestimated blood loss by 33% compared with assessment using the drape, and the authors concluded that in low resource settings more accurate measurement of blood loss using a drape (or similar low cost method) could greatly reduce maternal death by allowing women to receive quicker treatment.

In developing countries where the incidence of postpartum haemorrhage varies between 5% and 20%, tools for the measurement of blood loss can be used to standardise timing of administration of an intervention, decide when to refer the patient, and plan for administration of additional interventions. Thus, research to help identify culturally acceptable blood collection methods, determine their accuracy and generalisability to various populations, and train providers on their use should be encouraged. By facilitating the timely diagnosis of postpartum haemorrhage, even during home births, such interventions can help manage postpartum haemorrhage and prompt referrals in a timely manner, ultimately helping to reduce the high associated mortality in the developing world.

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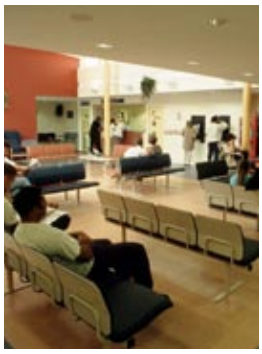
Rising hospital admissions

Can the tide be stemmed?



SHOUT/ALAMY

Stephen Gillam general practitioner, Institute of Public Health, Cambridge CB2 2SR
sjg67@medschl.cam.ac.uk

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Whoever wins the next election, years of famine are upon us. Budgetary belts are tightening in anticipation. All the more disquiet therefore attaches to a report from consultants Caspe Healthcare Knowledge Systems (CHKS; an independent provider of healthcare intelligence and quality improvement services) that, "threatens bankruptcy for the NHS."[1]

The growth in hospital admissions for elective and emergency care apparently rose by an average of 6% in England between 2007-8 and 2008-9.[1] This compares with an average annual growth of 4.6% for the preceding three years, and it is mirrored by similar rises in Wales and Northern Ireland. Emergency admissions, which are inherently less susceptible to manipulation and therefore the main cause for concern, formed the bulk of these increases. Three simple questions present themselves. Firstly, are these hospital episode statistics reliable? Secondly, if so, what is driving these increases? Lastly, what can be done to reduce unnecessary use of hospital services? Unfortunately, the answers are not so straightforward.

Hospital admission rates have long been of concern. Earlier supposed increases in emergency admissions were mainly attributable to internal transfers after admission.[2] The figures have also been artificially boosted by coding differences and the conversion of patients who exceed the four hour emergency care waiting target into admissions, but this seems unlikely to explain these rises. Short stay admissions may account for much of the surge in emergency admissions.[3]

To some extent the NHS is a victim of its own success. Increasing capacity and shortening waiting times have probably increased public expectations and lowered referral thresholds. Demographic change is tending to increase healthcare needs in older age groups. Political rhetoric that promises choice has encouraged the use of health services while simultaneously requiring frontline practitioners to contain exactly those expressed needs. Fragmented out of hours primary care was one predictable consequence of the contract for general practitioners introduced in 2004. Seasonal factors affect admission rates for respiratory and other conditions, but subtler influences may be contributing.

A multitude of new access routes (from nurse led community based services to NHS Direct) have eroded the gate keeping function of general practitioners. The advent of the quality and outcomes framework is likely to have had paradoxical consequences. Improving the quality of chronic disease management should reduce hospital admissions, but the incentives to identify and treat earlier disease may counter this. The labour of once expert generalists is being divided among salaried doctors, specialist nurses, and others. What might be termed the "clinicisation" of general practice—polyclinics in process if not in structure—is compromising continuity of care and reducing access to just those practitioners who may be able to contain and manage comorbidities in the community.

This year emergency admissions in excess of baseline 2008-9 values will attract only 30% of the relevant tariff, thereby reducing hospitals' incomes. It remains to be seen how marginal tariffs will affect activity rates. So what else can be done to reduce demand for hospital admissions? The answers often involve general practitioners.[4] If they can be persuaded to improve their management of "ambulatory care sensitive conditions"[5] and reduce referrals (for example, for elective conditions by use of structured guidelines), admission rates may be reduced. Various reviews have examined the research in support of different approaches to demand management (box).[6] Suffice to say, the evidence is limited.

The CHKS analysis showed large variations between different primary care trusts. Fifteen saw cuts in their admissions for 2008-9, but little is known about why. Attempts by primary care trusts to drive down referral rates have involved the use of local enhanced services agreements that link payments to target reductions. It is hard to envisage an equitable system of referral quotas given the quality of most referrals data, which are not adjusted for age and sex differences between practice populations. Other widely used approaches are general practitioner services in the casualty department and local referral management centres.[7] Disappointingly few evaluations of local policy initiatives are available to guide commissioners. Without a clearer understanding of causes and solutions, crude systemic responses may generate perverse consequences for patients, breaching the principle of treatment according to greatest need.

Practice based commissioning affords potential levers to provide early intervention in the community, but savings in secondary care expenditure are seldom visible. Not surprisingly, enthusiasm for commissioning is limited. General practitioners are reluctant to accept liability for overspends for which they do not feel responsible. Conservative proposals to firm up budget holding at practice level are one favoured solution, but the effect of fund holding on referral rates was equivocal.[8] More radical alignment of financial incentives would involve capitated budgets for all primary care and secondary care in a similar manner to integrated care organisations in the United States.[9] This would help relocate many hospital based specialist services into the community.

With the NHS facing a projected shortfall of £8.4bn (€9.7bn; $13.4bn) for 2010-1,[1] politicians must be hoping for patient restraint in times of austerity; simply telling the public how much an inappropriate visit to the accident and emergency department costs would be a start. Tough measures may indeed be part of the solution; on the "burning platform," the previously unthinkable (hospital closures) may become acceptable. In the meantime, prepare for longer waiting times.

Approaches to reducing unplanned admissions with a limited evidence base

- Education in self management
- Managed care programmes
- Integrated health care and social care
- Coordinated discharge planning
- Multidisciplinary case management
- Specialist nurses
- General practitioners in the accident and emergency department
- Referral guidelines
- Referral management centres
- Telecare

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BMJ policy on data sharing

New guidance proposes minimum standards to lessen risks to participants' privacy

RESEARCH METHODS AND REPORTING, p 304

Trish Groves deputy editor, *BMJ*, London WC1H 9JR
tgroves@bmj.com

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The *BMJ* asks authors of original research articles to state in their manuscripts whether they are making available any additional unpublished data. These may comprise raw unprocessed data as well as protocols, analyses, statistical codes, images, and ideas (http://resources.bmj.com/bmj/authors/types-of-article/research). We ask this largely because we are keen to maximise the usefulness and usage of data and promote transparency, but also because many research funders now encourage or even mandate data sharing.[1] Many *BMJ* articles' authors simply say "no additional data available," but a growing repository of positive data sharing statements range from "an audit trail of the forest plots and related data is available at www.wolfson.qmul.ac.uk/bptria"[2] to "a full list of participants' quotes and explanations offered by the authors to illustrate each of the four themes are available on request from the corresponding author at rachaelm@health.usyd.ed.au."[3] We are delighted that authors have been so willing to share data.

We appreciate that the acceptability and practicability of this concept will vary among studies and authors. The ethical and legal risks to the privacy of patients and other participants are important and must be taken seriously. Even among those who are willing to share data, some may want to defer this until after a period of fair use, and some may limit sharing only to other researchers, perhaps on personal request or at a password protected website.

In the linked article, Hrynaszkiewicz and colleagues advise researchers to seek informed consent to data sharing from research participants upfront, at the recruitment stage. They also point out that until now there has been little information on how such data should be prepared for sharing.[4] As well as discussing technical aspects, they list 28 personal and clinical descriptors that could de-identify patients. These descriptors are derived from a review of policy documents and research guidance from major UK and US funding agencies, governmental health departments and statutes, and three internationally recognised publication ethics resources for editors of biomedical journals. They recommend that direct identifiers such as names should be removed from datasets and urge caution with using indirect identifiers such as age and sex. These items are often needed to make sense of the science and, on their own, pose little risk to confidentiality. In combination, however, they can build a recognisable personal profile.

So Hrynaszkiewicz and colleagues and the working group they convened (which included TG) are recommending that datasets containing three or more indirect identifiers for any participant should be reviewed—either by an independent researcher or even by an ethics committee—to assess this risk before being shared. This, they say, should be the minimum standard for ensuring that participants' privacy is not put at unnecessary risk. They also recommend that authors should make explicit statements about consent in research articles that have linked raw data. They suggest that authors choose one of three options, stating either that participants gave informed consent for data sharing, or that consent was not obtained but the presented data are anonymised and risk of identification is low, or that consent was not obtained and the dataset does pose a threat to confidentiality. (This last option is, clearly, controversial.)

The *BMJ* does not intend, at least for now, to post additional large datasets online. But we will continue to encourage authors to link their *BMJ* articles to such data deposited elsewhere, and we are now adopting some of the recommendations made by Hrynaszkiewicz and colleagues. Firstly, we strongly support the view that researchers should seek informed consent to data sharing from research participants upfront, at the recruitment stage. There are good ethical and practical reasons for doing so. Even if the investigators have no current plans to share raw data, at some future time data sharing may become the norm. If so, sharing will be much easier if no one has to try to seek consent retrospectively. Secondly, we will expand our advice to authors about data sharing to reinforce the need for anonymisation and to warn authors of the 28 patient identifiers they need to consider. And, thirdly, we will extend our data sharing statements to include explicit information about consent.

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