

## ESSAY

# The rise and fall of infant reflux

The limits of evidence-based medicine

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**AT** the dawn of the twenty-first century Queensland infants were in the grip of an epidemic. Babies screamed, vomited and woke frequently at night. They refused to feed, arched their backs, drew up their knees. Parents were frantic: even if they could soothe the flailing fists and the little crumpled face, the minute they put their baby down, the piercing shrieks began again.

Once, we called this colic. We attributed it to wind, and a woman struggled through the nightmarish first months of a colicky baby's life without much support from health professionals or even sympathy from those around her, secretly and horribly convinced of her own public failure. But by 1982, when a small group of 'reflux mums' formed the Vomiting Infants Support Association of Queensland, the nascent sub-specialty of paediatric gastroenterology had found in colic a *cause célèbre*.

The association went national in 2000 and became RISA, the Reflux Infants Support Association, aiming to give confidence and moral support to families of infants with problems associated with gastroesophageal reflux. But the epidemic appeared to be at its worst in Queensland, a state prone to statistical exaggeration. One prominent Queensland paediatric gastroenterologist pioneered the link between infant irritability and gastroesophageal reflux disease (GORD), and took to the lecture circuit to raise professional and community awareness. He subsequently relocated overseas and remains a dedicated and caring doctor, but he saw the world, particularly crying babies, through a very special – specialised – lens.

I subscribed guiltily to *RISA News*. Throughout the 1990s, as the epidemic worsened, my own robust offspring grew into preschoolers, then primary schoolchildren. They never cried much and, as the newsletters explained, only the parents of a reflux baby can truly relate to the exhaustion, despair, headaches and lack of sleep. But I'm a GP, and throughout the 1990s until the mid-2000s infant GORD was rampant. Many of the babies I saw came pre-diagnosed with 'reflux' by the paediatrician, the hospital midwife, the child-health nurse, the breastfeeding counsellor, or the lady across the road. New mothers stepped carefully into the consulting room, manoeuvring the pram through the door or lugging the car capsule or carrying the baby, sat down in the chair by my desk, and wept.

Babies from the first days and weeks of life were being given cisapride, ranitidine or cimetidine, antacids – often in double doses – and, from the end of the decade, proton-pump inhibitors (PPIs). An American study showed that PPI use in infants multiplied sixteen-fold between 1999 and 2004.

In the *Australian Family Physician*, *Medicine Today* and *Australian Doctor*, diligent GPs read educational articles about crying babies and GORD written by paediatricians and gastroenterologists. Parents were angry with any incompetent practitioner who 'missed' the diagnosis. They were especially angry with the hapless doctor who ventured that maybe the baby was just a bad sleeper, or that the mother was unnecessarily worried. Having a new baby is not the blow-waved, lacy-white sensuality of the Lux mother: a brutal collision with reality lurks beneath the sentimental images of motherhood, shocking us early on, and it's reasonable to expect a sensitive response from the GP. But parents came to believe that a failure to diagnose was a failure to care.

In the A4 newsletter that arrived in my mailbox every couple of months I read a stream of heartbreaking testimonials, alongside hints on sterilising medicine cups and removing the smell of vomit from clothing, or recipes for blancmange to thicken expressed breast milk or formula. There were diagrams illustrating how to change nappies with a pillow under the baby's shoulders and without lifting the baby's legs, or how to breast- or bottle-feed holding the baby vertical. There were ads for approved cot harnesses to secure the baby once the head of the cot was raised thirty degrees, or for slogan T-shirts, cheap and cute, for the discernible [sic] 'reflux' baby, alongside order forms for a

fundraising drive. Contributions from paediatric gastroenterologists and GPs advised frequent burping, thickened breast milk, thickened formula, frequent breastfeeds, spaced breastfeeds, different bottles, different formula.

It felt voyeuristic, peering into the newsletters like this, browsing families' misery and their plucky attempts to keep each other's spirits up, all written in homey prose. But it was also clear to me that Queensland babies, at least in the first few months of life, were in the grip of an imaginary disease. It's true that premature infants, and infants with certain underlying health problems, for example, neurological abnormalities, are prone to GORD. But in otherwise healthy, full-term babies in the first few months of life, excessive crying, crying in a piercing shriek, back-arching, turning red in the face, flexing up the knees to the tummy, disrupted sleep, vomiting, and crying when put down are common behaviours, not caused by pain or reflux. I could see that using the diagnosis of GORD to explain these behaviours caused harm to mothers and babies.

For a start, parents were desperately focused on performing the various odd, disruptive and time-consuming manoeuvres supposed to protect their baby's imaginary oesophageal lesions. These preoccupations certainly didn't help parents learn to read and respond to their infants' cues. Yet learning to read and engage the baby's communications (a difficult task in unsettled babies, one that may even require professional help) is a very important way of protecting the mother-infant relationship and the child's long-term mental health.

Multiple other problems were often not identified or addressed in the frenzy of activity surrounding GORD: for example, feeding difficulty, cow's milk allergy, maternal anxiety or depression, or lack of familial and social support. Worse still, if correctable clinical problems weren't diagnosed, mothers and babies were at risk of developing entrenched, long-term problems, including ongoing feeding difficulties. The consequences of undetected and unmanaged feeding difficulties may be catastrophic for some, resulting in severely disrupted and anxious mother-infant relations, since it is not easy for a mother to remain calm at feed times if she believes her baby is starving.

Some babies do develop true GORD down the track. Could it be that by over-diagnosing GORD in the first few months of life, we also predisposed

some babies to oesophagitis later on? This is a sensible interpretation of what we know about the multiple factors that do predispose babies to GORD, and the effects of failing to identify them.

Worst of all, cisapride (trade name Prepulsid) could fatally disrupt the beating of a tiny heart. This was recognised in 2000, after two children died. But the potential for disaster didn't halt the GORD juggernaut: we simply substituted PPIs, even though they had not been trialled on a large scale, over time, in infants in the first weeks and months of life.

AS A GP, I specialise in generalism. I started my professional life in the turbulence of an Aboriginal and Islander Community Health Service, which alerted me to other frames of reference, including to cross-cultural differences in infant care. I have a better-than-average grasp of the physiology of lactation, of breast-milk substitution and the infant gut, because I qualified as an international-board-certified lactation consultant when I had my babies, in snatched hours while they slept. Many GPs, paediatricians and paediatric gastroenterologists remain inadequately educated about breastfeeding, and even midwives and child-health nurses have variable standards of skills in lactation support. These knowledge deficits, the problem of the health professional who doesn't know what he or she doesn't know, are significant for unsettled babies.

Clinical epidemiology is a branch of medicine that expanded dramatically in the 1980s. It aims to understand patterns of disease and the way treatment changes these. The most authoritative of its analyses, the randomised controlled trial (RCT), assesses the effectiveness of interventions by making two populations as similar as possible, then comparing them, with and without the added intervention, applying statistical analyses to assure us that these changes didn't occur by chance. In 1992, a group of academics at McMaster University in Canada took clinical epidemiology and repackaged it as 'evidence-based medicine'. In their manifesto they proclaimed EBM a paradigm shift, a revolution. They critically ranked the quality of research, eliminated much of the poor science, and developed tools for synthesising the results of multiple trials. They were 'manning the barricades' against the

health professional who did not know what he or she did not know. They had chutzpah (hubris, their critics called it), and began harnessing the explosion of digitally available research with clever inventions like specialised databases, search filters, hierarchical ranking of evidence, systematic reviews and meta-analyses.

Like all good brand-makers they were revisionist, claiming to cleave the history of medicine into the pre-EBM era of dangerous, expert-led, opinion-driven, inconsistent care, and a post-EBM era that was clear-eyed and modern, pragmatic and anti-authoritarian. A democracy of evidence, except (so the critics complained) the EBM men set the rules. Brand EBM became a catchcry, a simplified and highly successful approach to health research that was rapidly co-opted by politicians and governments. Massive funds were diverted to the cause, and academic careers took off. Eighteen years later, critics are still scathing. A zombie, or a dead fish swimming, they call it, arguing that EBM has long since been exposed as a very limited approach to health knowledge: dead in the epistemological sense, but made to act as if alive because it's inflated with funding and bouncing about.

All of this has had a remarkable effect on the culture in which I've practised over the past twenty-five years. Three-quarters of all medical consultations in Australia are with GPs, and most Australians consult their GP once a year, yet general practice research has always been drastically underfunded. Despite remarkable gains in the past decade, it is still, as a result, fifty times less productive than research in, say, internal medicine or surgery. From the late 1990s a handful of general practice academics in Australia became preoccupied with the fight to improve general practice's credentials, trying to secure a foothold in a clinical research landscape utterly dominated by hospital-based specialists (who have been at times referred to in primary care as partialists). In the real world of general practice consultations, where the messy stuff of patients' lives and contexts write into the body in dynamic and unpredictable ways, there are serious limitations to the usefulness of RCTs, but these powerful Australian EBM men were focused on making up ground. Genuine conservatives (or are they the genuine radicals?), thoughtful about the nature of evidence and its place in the complexity of primary care, struggling to articulate an authentic clinical practice, were brushed off as out of touch.

By the time the GORD epidemic really took hold in crying babies, doctors were expected to follow brand EBM unquestioningly. A vigilant moralism about how we practise came to the fore.

So what do you do when you are confronted by an expectation that you practise according to the ‘evidence’ – an agreed clinical protocol written up in authoritative, peer-reviewed journals – when the evidence contradicts what you have reason to believe, from your own transdisciplinary knowledge base, is in your patient’s best interests? Diverging from accepted best practice is professionally compromising, even dangerous. But not contesting a harmful diagnosis is ethically compromising, dangerous to one’s personal integrity and peace of mind, not to mention patient health. I found this cognitive dissonance across a range of issues acutely painful. It seriously compromised my capacity to enjoy general practice. Finally, I took up research – an act of subversion.

But what madness was it to spend my limited free time, over the years, doing searches of the Medline or PubMed or CINAHL databases, poring over papers about my chosen issue: infant crying and GORD? Why did I lock myself away that warm outback Easter, when the kids played with their cousins in the red dirt amid tailings of freshly picked cotton, to read accounts of RCTs and cohort studies in the *Journal of Pediatric Gastroenterology and Nutrition*, or the *Archives of Disease in Childhood*, or the *Journal of Gastroenterology and Hepatology*?

A set of shared assumptions that were implicit and unquestioned screamed at me from the hundreds of papers I read, like babies no one wanted to pick up. First, the research assumed that a clinical sign or problem must result from a disease: the reductionist, ‘biomedical’, cause-effect paradigm. Second, the research assumed that certain infant-care practices in our society were biologically normative: that is, they could not impact on infant behaviour and physiology, and did not need to be taken into account or controlled for in clinical trials. Third, the research assumed that findings in toddlers and children could be generalised to newborns and babies in the first months of life. These assumptions ignored entire disciplines: for example, lactation research exploring the differing effects of formula and breastfeeding on gut physiology, or research in neurology exploring the relationship between the autonomic nervous system and gut physiology, or in ethnopaediatrics

exploring cross-cultural differences in infant care, or in developmental psychology exploring the interrelationship between sociocultural factors, parental health and the maturing architecture of the infant brain. Nomenclature in the literature concerning infant GORD was seriously confused, since normal physiological events were interpreted as disease processes; and, due to basic misunderstandings about the way feed-spacing affects the acidity of reflux, the usefulness of the researchers' investigative tools were hopelessly compromised. This all seemed obvious to me, as a generalist; but I was critiquing a powerful and prestigious body of international experts.

IN 2004, I applied for funding through the Primary Health Care Research, Education and Development Strategy, which had started in the 1990s as the General Practice Evaluation Program. To date, the PHCRED Research Capacity Building Initiative has been the federal government's main contribution to the development of primary-care research, administered by twenty-six university departments around Australia. A PHCRED Novice Research Fellowship remunerated me for a day a week of research over twelve months.

I published an analysis. The night an email arrived saying my article had been accepted, my husband uncorked a bottle of champagne and toasted me over dinner. 'Good on you, Mum, we're really proud,' my adolescents chorused, having figured out that this was my equivalent of winning the soccer championship or playing a violin solo in the school concert. My son raised his glass with so much enthusiasm that his milk spilt.

But my kind of analysis was out of fashion. Nobody was much interested in thinking about clinical problems; they just wanted the results of trials. Now you've got to build on it, my loyal husband said, but I was disheartened. Too many Easters lost, too many novels unread, too many good movies missed. Every time I saw an unsettled baby at work, I felt a jolt of grief.

Finally, once my daughter left home, generous supervisors allowed me to devote one morning a week of my part-time university teaching appointments to research. I began the task of developing an integrated, multidisciplinary, primary-care approach to unsettled babies and their mothers. Synthesis of transdisciplinary perspectives is a unique skill of the GP, so I began reviewing

the extensive bodies of literature from various disciplines dealing with crying babies. This meant challenging traditional EBM approaches and drawing on innovative new methods that were more appropriate for complex problems. Cross-professional co-ordination of care is also a unique skill of the GP, so I aimed to network, interview key informants, and develop an integrated multi-disciplinary primary-care approach to unsettled babies and their mothers.

Midwives told me that continuity of care from the early antenatal period through delivery to six weeks postpartum would address many problems that result in distressed mothers and babies. Child-health nurses told me that mothers of unsettled babies needed to be able to access their services in the community without long waits. Speech pathologists were concerned that babies with feeding difficulties should be seen before disrupted mother-infant relations entrench; lactation consultants argued that their services should be available promptly and affordably to all new mothers who need them; occupational therapists and physiotherapists pointed out that irritable infants may have sensory processing problems, and that sensorimotor integration should be considered. Psychologists and social workers wanted early identification of obstacles to mother-infant bonding and to a baby's healthy psychosocial development. Perinatal psychiatrists warned that early detection of and support for maternal anxiety and depression is vital.

When I presented my preliminary work at a general practice conference, a crusty old GP challenged me from the back of the room. 'Of course GORD occurs in crying babies from very early on,' he said. 'You should see the relief on a mother's face after a day or two of PPIs.' I explained that any medication for unsettled babies had a 50 per cent placebo effect. 'I listen to the mothers,' he replied bluntly. As if I didn't!

But I admired his spunk. He was the type of old-school GP driven crazy by brand EBM, which expected him to treat that mythical standardised patient, who is everybody and nobody. Many GPs felt that EBM, at least until it began to revise itself, devalued the individual needs and autonomy of the patient, and the experience of doctors, in the name of pure 'evidence'. It's often said that's why GPs don't engage in research, although it might just be that they are simply overwhelmed by patients and bureaucracy, without the kind of income that makes time for unpaid research possible.



‘So many unsettled babies are still on PPIs,’ mused a cheerful, firmly spoken social worker from a large children’s hospital down south, a woman about my own age whom I met at an infant sleep roundtable last year. ‘I thought we put a stop to that!’ Shortly after my first paper came out, she’d published a landmark study with a bunch of paediatric gastroenterologists and paediatricians showing that anti-reflux medications had the same effect as placebo in crying babies. Their widely cited RCT marked the peak of GORD in unsettled infants. But an RCT also side-stepped the need to think about why the epidemic had taken hold. I worried that if we didn’t think analytically about the GORD epidemic in crying babies, if we didn’t critique our theoretical frameworks and mistakes, the same errors would be repeated.

AFTER MY PRESENTATION at that Queensland conference, an amiable professor suggested a cup of tea at the long table set with urns, fruit platters and scones. I’d met him in 2004 when I first wandered into the Centre of General Practice talking about crying babies. He’d pulled a strange wooden contraption out from among dusty boxes and folders in a basement storeroom and offered it to me. It measured a baby’s cry, he explained. He’d invented it as a young father when his own babies screamed inconsolably all night long. In 2004 he was a rising star, one of that handful of lean, bike-riding, surfboarding EBM men who stormed the brand-new discipline of general practice research and lifted it out of its lethargic, government-induced preoccupation with surveys. In 2004 he couldn’t imagine serious research that didn’t measure things. He would stare at me blankly when I used terms like evolutionary biology. ‘Where’s the evidence?’ he would ask.

Brand EBM is better suited to the pharmaceutical, surgical and technological interventions of other narrowly focused specialties, though even there, as the GORD epidemic demonstrated, it has its limitations. General practice, however, demands more intellectual rigour of us than just that, since patients come in with complex, multidimensional and undifferentiated health problems, affected by many factors, known and unknown, dynamically interacting in that patient’s life, environment and social context. From the early 1990s I scrawled web-like diagrams on scraps of paper for my

patients: multiple things seem to be interacting and contributing to this problem, I would say. The problem might be depression, or fibromyalgia. It might be diabetes, or obesity, or chronic fatigue. It might be polycystic ovary syndrome, or tension headaches. It might be unsettled behaviour in a baby.

To my mind, intellectual rigour in general practice research asks us to draw on our unique generalist skills of integration and synthesis, our exposure to trans-disciplinary perspectives, the breadth and depth of our knowledge base, and our familiarity with a patient over time in their socio-cultural and environmental context, in order to think about complex problems. Then the investigative studies we draw on, or instigate, will be useful. Brand EBM is linear. A human being is not.

On the day of the conference, the professor who invented a cry-measuring machine looked up and paused as he stirred a spoonful of sugar into his tea. 'Why don't you just run a trial of cognitive behavioural therapy for the mothers?' he asked. 'That's what's needed when babies cry.' But any mother – including his wife, I expect – will tell you it's not so simple.

'The problem with your research is that you haven't started with an open mind,' another senior research fellow remonstrated, just months ago. 'You've got your own theories, then you choose evidence to fit them.' Attempts at theoretical framing arouse a kind of moral panic among diehard EBM advocates, as if you are embarrassingly airy-fairy, even intellectually inferior and somehow unfit. A quack. 'Evidence-based medicine is about the open mind, no preconceptions' – this person made it sound like zen, a pure spirit, a state of true inquiry – 'and then you rank the existing RCTs according to quality and do a systematic review. That's how you get the answer.'

What could I say? This lack of insight into one's own unconscious theoretical bias was the reason we had an infant GORD epidemic in the first place! And if we don't develop and debate theoretical frameworks, then we don't know which questions to ask, which ones are most targeted and cost-effective. We pluck research questions out of the air, blindly. Critics argue that EBM, so proud of its 'pragmatism', remains blissfully unaware of its own implicit theoretical assumptions and is, therefore, unable to engage criticism rationally. It doesn't know what it doesn't know. Brand EBM is, therefore,

a fundamentalism. You believe in it. You don't have to know what other disciplines, for example, the social sciences, are saying about an issue. You can avoid the headache of complex clinical problems and focus on the simple ones, amenable to straightforward cause-and-effect interventions, which translate into more publications and a successful career. 'EBM is a very odd approach to knowledge,' confided another professor of primary-care research, from down south, 'and it's influencing policy in worrying ways.'

Then my proposed study won the RACGP Research Foundation's most generous bursary: \$20,000 for research costs. I'd written the application over yet another Easter, this time on Stradbroke Island, looking out on the stormy skies and crashing surf at Main Beach, with my daughter and her boyfriend sleeping in and my son down at Cylinder Beach looking for girls. When I won the scholarship, I googled the professor who died so young and bequeathed this fund for those starting out in primary-care research. I felt a sudden burden of responsibility to make him proud, to make a difference. He was an EBM man of formidable intelligence and charisma, and I like to think that, if he were still here, he would understand what I'm trying to do.

IT WOULD BE disingenuous to frame my research into crying babies as a struggle between brand EBM and complexity in primary care, using the same tired old oppositional discourse – though I confess it has often felt as if it is that. But integrating the mass of digital-age research into unsettled infant behaviour, and generating high-quality information, would not be possible without brand EBM. Every time I search the literature, every time I appraise a study for rigour, every time I look for the highest level of evidence, I benefit from its legacy. Even the form of literature review I have used, metanarrative mapping, was first formalised in the UK by a feisty professor of general practice, wrestling publicly with both the benefits and limitations of EBM.

The GORD epidemic is best framed as a by-product of reductionism in medical research, the same reductionism that proved fertile ground for the rise of brand EBM. Reductionism is an extremely useful tool for highly specialised, hospital-based research interests, and the GORD epidemic in unsettled babies can be understood as a hot-headed moment in the youthful

discipline of paediatric gastroenterology research that got seriously out of hand. But reductionism alone fails to make sense of the breathtakingly complex, stunningly unpredictable, constantly dynamic problems that a GP in the community encounters in her consulting room every day.

Perhaps we needed a final burst of medical reductionism at the beginning of the twenty-first century to sharpen our critical thinking about the way forward into an increasingly complex future in healthcare. EBM advocates have expanded definitions of the 'E' to address their critics' complaints: 'E' includes, now, many other forms of evidence besides RCTs, including qualitative studies, and these days EBM has abdicated absolute authority and modestly aims to serve the patient and the clinician. Perhaps it could be said that EBM in its new, revised form is helping dismantle the infant GORD epidemic like the Ouroboros, the snake swallowing its tail – what began it also ends it.

But critics remain scathing, declaring that brand EBM is intellectually dishonest in its attempts to appropriate the much greater enterprise of understanding and improving health. It was a masculinist project, they argue. It's had its moment, left its legacy. This is the era of complexity, of personalised, patient-centred medicine, critics maintain, and brand EBM is dead.

Meanwhile, the diagnosis of GORD in unsettled babies in the first months of life is waning, although it's still surprisingly common. Now, more and more breastfeeding mothers of unsettled infants see their GPs on complicated elimination diets, interspersed with food challenges. Mothers pore anxiously over food diaries, explaining which foods have passed through their milk and upset their babies. Or they detail the various formulas they've tried. Food-allergy babies are waking frequently at night, crying excessively, crying in a piercing shriek, arching their backs, turning red in the face, flexing the knees up to the tummy, vomiting, refusing to feed.

Once again, parents are frantic. Conscientious GPs read articles about food allergies written by other specialists. It's dramatically increased in incidence over the past two decades in older children; it's a lifelong illness; it requires constrained diets and swallowed steroids; it may result in oesophageal strictures if untreated. But we are making the same old mistake of

extrapolating back, diagnosing food allergies in irritable babies and prescribing PPIs in addition, just to be on the safe side.

Using the tools generated by brand EBM, we can say with confidence that the incidence of cow's milk allergy is increasing, and is a cause of unsettledness in babies. But the evidence that food allergies more generally cause unsettledness in babies in the first few months of life is unconvincing. This diagnosis appears to be another reductionist solution offered to distraught parents by concerned health practitioners in the absence of an accessible, multidisciplinary, primary-care approach.

Because health systems with strong primary care are more efficient, have lower rates of hospitalisation, fewer health inequalities and better health outcomes, the Australian government has promised to make primary care its central plank in health system reform. The Department of Health and Ageing is closing down the PHCRED Research Capacity Building Initiative at the end of 2011, channelling funds into a small number of Centres of Research Excellence in primary care, so that teams of mostly postdoctoral researchers can focus on multidisciplinary collaboration, the translation of research into practice, and policy, according to priority themes. But some senior figures fear that the funding pool for primary care research is contracting with the closure of the PHCRED Research Building Capacity Initiative, and that it will be even more difficult for researchers starting out, like me. Certainly everyone in primary care research agrees that if there is to be any seriously effective health system reform, primary care research desperately needs more funding.

IN THE ABSENCE of an easily accessible, multidisciplinary, primary-care approach, it is more likely that the mother of that crying baby next door may cease breastfeeding prematurely, that she may require treatment for postnatal depression, that the baby may be abused in a moment of terrible and frantic overwhelm, that the baby may require treatment once it reaches school age for long-term psychological and behavioural problems.

Recently two internationally prominent gastroenterologists published a paper proposing that acid-suppression medications predisposes babies to

food allergies. They cite research showing that a less acidic environment in the stomach prevents breakdown of complex proteins, at the same time as the medications increase the permeability of the gut. Absorption of undigested proteins sensitises the immune system. They argue that the dramatic rise in prevalence of food allergies over the past two decades fits with the exponential increase in the use of PPIs in this time.

So, worse still, it seems quite possible that an epidemic of an imaginary disease in unsettled babies has created, through unnecessary medication, the misery of lifelong food allergies for some. This is a high price to pay for crying out.

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