EDITORIALS

Turmoil over New Delhi Metallo-Beta Lactamase-1: a tale of ersatz patriotism

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Much ado about nothing *(Shakespeare)*

Gone are the heady days of the 1960s when we tramped around town on August 15 with a tricolour in hand and a song on our lips. By the 1990s, patriotism was passé and it was clearly "uncool" to become sentimental on Independence Day. After all, why waste a hard-earned holiday moping over impulsive young people who went to the gallows in a quixotic gesture against the might of the Empire?

So we fogeys learnt to move with the times in tune with the mantra "Consumerism is cool, patriotism is for fools", until we were rudely shaken up on August 12 by a burst of jingo louder than anything since Kargil. What was the matter? Independence Day was up close, no doubt about it. But it was not a golden or a diamond Independence Day to merit all that noise. Believe it or not, it was over an enzyme. The enzyme, unfortunately named New Delhi Metallo-Beta Lactamase-1 (NDM-1), enables Gram-negative bacteria to break down broad-spectrum antibiotics called carbapenems. Bacteria that break down carbapenems can be very difficult to treat and only at a cost that few Indians can afford.

The enzyme is encoded on a circular piece of DNA that has a penchant for jumping between bacteria. And the bacteria, in their turn, love to hitchhike across continents in the wounds and intestines of the clients of India's ambitious medical tourism industry. As long as the enzyme was content to live within India and kill hapless Indians, nobody cared. All hell broke loose when the enzyme developed a taste for foreign travel, got a catchy name, and, finally on August 11, 2010, got itself splashed on the cover of *Lancet Infectious Diseases* (1) that in the world of bacteria has the same glamour quotient that *Vogue* has in ours.

What's in a name? *(Shakespeare)*

Lots of people are sore about the fact that the enzyme has been named after New Delhi. Well, to the best of my knowledge, this is the first time a beta-lactamase enzyme has been named after a place. But there are examples galore of pathogens being named after places. After all, who doesn't know of Japanese encephalitis? The Chinese didn't complain of a conspiracy to tarnish the fair name of the Middle Kingdom when the predominant strain of *Mycobacterium tuberculosis* circulating in East and South-east Asia was named the Beijing strain (2). Lyme disease is named after Lyme, Connecticut, USA, and the Norwalk virus (now Norovirus) was named after Norwalk, Ohio, USA. There are numerous serotypes of *Salmonella enterica* with names like "Dublin", "Heidelbergensis", "Saintpaul", "Newport", etc. Nobody till date has had problems with names like Spain23F-1 or Sweden15A-25 given to multi-resistant clones of *Streptococcus pneumoniae* (3). There was no trouble in 1992 when a new serogroup of *Vibrio cholerae* got known worldwide as *"Vibrio* cholerae O139 Bengal" after it spread along the Bay of Bengal littoral with consummate ease (4).

Seek and ye shall find *(The Bible)*

In fact, if we think of it, most of these place names are from countries in the developed world that have a strong network of public health laboratories with the ability to isolate and identify novel pathogens. So, it ought to be a matter of pride, not shame, to have a pathogen named after one's hometown or country.

It is a sad reflection on our developmental priorities that some recent steps taken by the government have actually curtailed our ability to keep vigil on important pathogens. The Central Research Institute (CRI, Kasauli) used to be a supplier of antigens for the diagnosis of typhoid fever and brucellosis as well as antisera for the identification of *Salmonella serotypes* and *Vibrio cholerae*. The quality was great and the prices were affordable; for about Rs 15,000 I could stock up on all the biological reagents that I would need in a whole year. By January 2008, CRI was no longer making these antigens and antisera (5). The price of procuring the same reagents from abroad was 10 times higher, way beyond the shoestring budget of my low-cost laboratory. So I simply learnt to do without them. And that gave local health officials one more excuse to question the authenticity of Vibrio cholerae isolations from our laboratory. Convincing them was difficult at the best of times; now it became impossible. It seems like Indians can never have cholera; they are only allowed to have gastroenteritis. Similarly, they never die of starvation; they only get permission to die of malnutrition. And they never die of falciparum malaria; they are only allowed to die of cardio-respiratory failure and a

hundred other causes except falciparum malaria. Woe betide the hospital where anybody dies of falciparum malaria; the entire local administration descends on the place to haul the doctors over coals. And now, I am sure, NDM-1 will be added to the list. Microbiologists will soon be forced to communicate the results of Meropenem sensitivity testing to their clinical colleagues either verbally or through sign language for fear of being accused of endangering national honour. And Meropenem testing disks will be made available only to hospitals with impeccable credentials staffed by patriotic microbiologists vetted by the CID (6).

You may delay, but time will not *(Benjamin Franklin)*

To look at the origin of carbapenem resistance in India, one has to go back to the last two decades of the 20th century and start with resistance to third generation cephalosporins, the workhorse antibiotics in most hospitals. Extended-spectrum beta-lactamase (ESBL) enzymes, which enable Gram-negative bacteria to hydrolyse third-generation cephalosporin antibiotics, were first detected in Germany in 1983. The first report of ESBLs in India was from Christian Medical College, Vellore, in 1995 (7). By the turn of the century ESBLs had stepped out into the countryside. By 2006, Lucknow had more than 60 per cent of its community-acquired *E. coli* producing ESBLs. By 2007-8, I was isolating ESBL-producing *E. coli* in our rural hospital in Chhattisgarh from patients who had never been admitted to hospital.

Many ESBL-producing bacteria carry genes for resistance to other antibiotics and the only antibiotics that were consistently effective against them were Amikacin and the carbapenems. Now, the logical thing to do in this kind of a situation would have been to reserve these two drugs for patients who were dangerously ill and treat the other patients on the basis of their culture and sensitivity test reports. (It is interesting that these bacteria sometimes turn out to be sensitive to old and inexpensive medicines such as Cotrimoxazole, Chloramphenicol or Nitrofurantoin; somewhat like David killing Goliath with his slingshot.) Unfortunately, most chose the easy way out and started using carbapenems as drugs of first choice (8). These precious reserve drugs quickly became routine drugs, not only in tertiary care hospitals and intensive care units but also in community practice, provided the patient could afford it. (A single course of Meropenem can wipe out the resources of a poor family.) Once that happened, it was only a matter of time before resistance appeared. And in the absence of a national resistance surveillance system, it spread right under our noses from hospitals into the community.

Reports on carbapenem-resistant Gram-negative bacteria have been piling up steadily from all over the country over the past few years, as the following data shows: They were isolated in Kolkata in 2002-3 (9), in New Delhi in 2004 (10) and in Mumbai in 2006-7 (11). In 2009, molecular characterisation for NDM-1 was done in Mumbai (12).

But did we, as a nation, act on these reports? No, we didn't, despite the fact that the report from Mumbai in the March 2010 issue of the *Journal of the Associations of Physicians of India* specifically warned of the potential impact of such resistance on medical tourism. Isn't it funny that the same thing that didn't hurt in March now suddenly hurts so badly in August? Is it because it comes from the land of our past rulers? Is it because the UK is the place where most of our medical tourists come from?

There is only one thing more painful than learning from experience, and that is not learning from experience *(Laurence J Peter)*

If we look outside extended-spectrum beta-lactamase enzymes (ESBLs) and metallo-beta lactamases (like NDM-1), we see the same story being played out in the field of other infectious diseases:

a) In tuberculosis, the incidence of mono-drug resistance among new cases in India for Isoniazid ranges from three to 32 per cent. The World Health Organization recommends that in populations with known or suspected high levels of Isoniazid resistance, new tuberculosis patients may receive HRE (Isoniazid-Rifampin-Ethambutol) in the continuation phase as an acceptable alternative to HR (Isoniazid-Rifampin) to avoid the selection or amplification of resistance (13). We still have not acted on the recommendation.

b) WHO recommended that Artemisinin derivatives be used only as part of combination therapy against *Plasmodium falciparum* to prevent the emergence of resistance. Yet, single-component, oral preparations of artemisinin derivatives continue to be available all over the country without a prescription.

c) Linezolid, the first member of a new family of synthetic antibiotics called the oxazolidinones, is supposed to be used as a reserve drug worldwide for infections caused by streptococci or staphylococci that are resistant to narrower-spectrum antibiotics such as penicillins (14). In India, Linezolid is even being prescribed to treat trivial skin infections.

Charity begins at home *(idiom)*

It is really irksome the way people are going on and on about the impact of NDM-1 on medical tourism. Don't NDM-1 producing bacteria infect Indians with equally dangerous consequences? Or should we understand that Indians don't count in their own country until they come back as "non-resident Indians" or "people of Indian origin" to patronise seven-star hospitals.

The conspiracy theory

Many people smell a rat behind the medical tourism alert, taking it as a deliberate blow to the reputation of our hospitals. To be fair to the British, all National Health Service (NHS) patients going into hospital for a relevant planned surgical procedure are screened for Methicillin Resistant Staphylococcus Aureus (MRSA) beforehand (15). This helps the NHS reduce the chance of patients getting an MRSA infection or passing MRSA on to another patient. Have we started doing that for ESBL or NDM-1 for our own patients?

Again, in the UK, if a patient infected or colonised with Vancomycin resistant enterococci (VRE) is transferred from one hospital to another, it is the responsibility of the medical staff caring for the patient to ensure that the receiving hospital/healthcare setting is aware of the VRE diagnosis (16). How many of our hospitals observe such niceties when transferring patients?

Finally, the National Health Service (NHS) or the Health Protection Agency (HPA) of the UK are not commercial organisations. So how can there be a clash of commercial interests in this case?

Touching concern

A senior health ministry official recently said, "It is a matter of concern if biomedical material can be transferred to foreign countries randomly. Like this, genetic mapping of our population can be done and exploited." (6) One would like to ask if the same official has any information on the size of the Indian diaspora, or on the number of people who are trafficked out of the country to the Middle East and South-east Asia every year. We are not talking of cells in test tubes here but intact human beings with at least 10 trillion cells per head. With so many cells at one's disposal, you can sequence them, map them, clone them, freeze them or do whatever else you want to do if you are brimming with malicious intent.

It wasn't until quite late in life that I discovered how easy it is to say "I don't know!" *(Somerset Maugham)*

Our honourable members of Parliament recently went beyond their charter when they "squashed on the floor of the Parliament" the article on NDM-1. Some parliamentarians went as far as "calling the report propaganda" (17).

The controversy could actually be funny except that it brought to the fore a certain lack of humility on the part of our lawmakers, the humility that enables one to say, "I don't know," the humility that makes one realise that election to parliament does not automatically give one the right to proffer an opinion on "cabbages and kings". Hitler is known to have had an opinion on everything ranging from what a good topic for medical research is to how a Beethoven symphony should be conducted. Some of our members of parliament (MPs) seem to be coming dangerously close. Let MPs make laws; let experts decide on the scientific merits of articles.

Conclusion

The fracas over the *Lancet Infectious Diseases* article focuses attention on our public health system or, rather, the lack of it; on the ease with which scientific issues can be hijacked by commercial lobbies and some politicians; and, most importantly, our foolish squandering of one of the most precious discoveries of the 20th century, the antibiotics, through lack of adequate stewardship. We hope we are able to keep science unsullied by the petty demands of partisan politics and keep national interest above business concerns if the two ever come in conflict. We also hope parliamentarians choose to restrict themselves to making laws and keep science in the hands of scientists. MPs with a background in science, may of course, choose to do both.

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Useful terms

Beta-lactams are a family of antibiotics that includes the penicillins, the cephalosporins, the carbapenems, and some odd members. They are the oldest family of antibiotics and still remain very useful.

Beta-lactamases are a family of enzymes that can break down beta-lactam antibiotics.

Carbapenems are beta-lactams with turbochargers. Members include Imipenem, Meropenem, and anything else ending in "penem". They act against a wide range of bacteria but are hideously expensive.

Cephalosporins are an older branch of the beta-lactam family. Members include Cephalexin, Cefuroxime, Cefotaxime and anything else beginning with 'ceph' or 'cef'. New members are still coming up.

Extended spectrum beta-lactamases are beta-lactamases that can break up third-generation cephalosporins.

Gram-negative bacteria are bacteria such as *E. coli, Klebsiella pneumoniae and Pseudomonas* aeruginosa, that become dangerous when our defenses are compromised. They also include bacteria like *Salmonella typhi* or *Vibrio cholera* that can bring down previously healthy people.

Metallo-betalactamases are beta-lactamases that have zinc at the active site to chomp up carbapenems. The notorious New Delhi Metallo-betalactamase (NDM-1) is one example.

Third-generation cephalosporins are cephalosporins with oomph that could kill a very wide range of bacteria until the ESBLs entered the scene.