

## *Salmonella* vaccine: a black sheep

Dipshikha Chakravorty

When Mary Mallon (a marvel comics character) known as ‘Typhoid Mary’ was taken away by the health officials for interrogation, she retorted by asking, ‘Why are you taking me away, when I am not sick’. Typhoid Mary was an excellent example of a healthy carrier who had spread the disease across many families as a cook. It is 100 years since then and nothing much has changed. Typhoid fever is the disease of the common man and has the capacity to cause arthritis<sup>1</sup>, endocarditis<sup>2</sup> and meningitis<sup>3</sup>. The extra-intestinal infections caused by *Salmonella* are fatal.

Systemic salmonellosis is a debilitating disease which can be life threatening. The global burden of typhoid fever is around 16–33 million cases as per WHO (World Health Organisation)<sup>4</sup>, resulting in 5–6 lakhs deaths annually. It is one of the best studied organisms in terms of its pathogenesis, yet the stealthy strategies employed by *Salmonella* largely remains a secret. Its ability to infect each and every tissue including the brain makes us believe that *Salmonella* is progressively becoming a successful pathogen. A wide range of available serovars and its ability to cause both localized and systemic diseases, points to the fact that *Salmonella* tries to paralyse the host in multiple ways. Finally, WHO has declared *Salmonella* as a bioterror organism under category B (ref. 5). In spite of the efforts which are taken to combat this disease, the vaccination against *Salmonella* has not been included in the vaccination schedule. The vaccine is limited either to the European and American travellers who travel to Asia or to army personnel. Currently, there are two vaccines in the market, Ty21a and Vi polysaccharide. Both these vaccines fall under the category of ‘fruits not to be eaten’. In early 1970s, chemical mutagenesis using nitrosoguanidine led to the discovery of Ty21a, which has GalE- and virulence (Vi) negative phenotypes<sup>6</sup>. Ty21a has been used with mixed success which varies from country to country. In Egypt, the trials demonstrated 95% protection rate after one dose<sup>7</sup>. In Santiago, where the typhoid fever is epidemic, the protection rate varied from 0% to 74%<sup>8,9</sup>. European tourists travelling to developing countries failed

to acquire protection against typhoid fever after vaccination with Ty21a (ref. 10). Moreover, this vaccine should not be administered to children, who are the most vulnerable group<sup>9</sup>. Purified Vi polysaccharide used as a vaccination can be a total failure as *S. typhi* strains are increasingly found to be Vi negative<sup>11</sup>. The question is what next?

*Salmonella* enjoys intracellular life and it is not sure whether the antibiotics can actually kill the bacteria which are hidden so deep inside the tissue. Drug resistance is an added burden. The latest antibiotic, ciprofloxacin is losing its ability to clear the infection due to resistance<sup>12</sup>. What is the reason that *Salmonella* has not drawn enough attention from the policy makers, though the number of typhoidal and non-typhoidal cases exceed that of human papilloma virus (HPV)<sup>13</sup>? Billions of dollars have been investigated to prepare a vaccine against HPV. Research shows that *Salmonella* has the capacity to defend itself against the innate and the adaptive immune arm. Its ability to counter defensins<sup>14</sup>, reactive oxygen species<sup>15</sup> and nitrogen intermediates<sup>16,17</sup> is well-documented. Its ability to inhibit antigen presentation clearly indicates that the host can never get protective immunity after *Salmonella* infection<sup>18</sup>. The survival of *Salmonella* in the presence of bile juice in gall bladder suggests its multifaceted homing strategies<sup>19</sup>. All these effects are brought about by very efficient two-component system (TCS), which can sense anything and everything from low pH, low nutritional status, alkaline pH to various oxygen and nitrogen stresses and toxic molecules<sup>20</sup>. *Salmonella* has further undergone horizontal gene transfer (HGT) thereby acquiring certain pathogenicity islands<sup>21</sup>. These pathogenicity islands make the bacteria invade, replicate and spread inside the stringent host environment. The availability of the whole genome sequencing revealed many virulence genes which may play a role in pathogenesis<sup>22</sup>. However, with such vast knowledge of *Salmonella* biology, what steps are being taken to eradicate this disease?

The poor ability to translate knowledge into development of either drug or vaccine suggests that it needs the sincere

involvement of researchers, medical professionals, health care workers, policy makers and investors. Bill and Melinda Gates foundation funded the DOMI program (diseases of the most impoverished) in five countries and since then the global impact on vaccine development against typhi and non-typhoidal *Salmonella* has increased<sup>23</sup>.

Researchers are working towards designing new vaccine candidates and the numbers of patents granted for vaccines against *Salmonella* are high. Many of these remain as glorified patents and never get translated. There are very few examples of phase 1 (ref. 24) and phase 2 (ref. 25) human trials with *Salmonella* vaccine. Our own vaccine candidate which has tremendous potential is waiting to get into human trials stage<sup>26</sup>. Hence, the question is how to tap a really potential patent and take it forward for trials and finally to the market? This will need a good team of basic researchers and industrial partners who can think in an unbiased way about the potentiality of the vaccine. The booming numbers of translational research institutes across the globe are inversely proportional to the number of successful vaccines for human use. The process of bringing the vaccine to market after ethical and safety approvals is very expensive. That may be one of the reasons why the basic research institutes cannot conduct human trials. Hence, the translational research institutes should have the facility to conduct human trials thereby bridging the gap between basic and translational research. We still do not have vaccines against *M. tuberculosis*, *Streptococcus*, *Staphylococcus* or *Salmonella*.

Every year emerging diseases like different kinds of flu (swine flu, avian flu) sweep across the country, thereby changing the priorities of the funding agencies. When these diseases subside, once again the focus shifts to chronic, persistent and debilitating diseases. Mortality rate alone is not a correct criterion to classify ‘the disease of the millennium’. More important than death is the disability adjusted life years. Crippled life is more expensive and burdensome than death.

Infectious disease programmes should have a strong aim to develop and launch

## COMMENTARY

---

the vaccine against infectious diseases at appropriate time and to develop new class of antimicrobials which cannot be countered by bacteria. Vaccination against typhoidal and non-typhoidal serovars should be included in the vaccination regime.

Till now *Salmonella* vaccine development has remained a black sheep! Hopefully increasing awareness and scientific endeavour will change the situation!

1. Girschick, H. J. *et al.*, *Clin. Exp. Rheumatol.*, 2008, **26**, S12–S17.
2. Al-Sherbeeni, N. M., *Saudi Med. J.*, 2009, **30**, 1091–1094.
3. Chen, T. L., Thien, P. F., Liaw, S. C., Fung, C. P. and Siu, L. K., *J. Clin. Microbiol.*, 2005, **43**, 5400–5402.
4. Initiative for Vaccine Research. Typhoid fever (accessed 23 August 2007; [http://www.who.int/vaccine\\_research/diseases/diarrhoeal/en/index7.html](http://www.who.int/vaccine_research/diseases/diarrhoeal/en/index7.html))
5. Pan American Health Organization, WHO, 13th Inter-American Meeting at the Ministerial level on health and agriculture, Washington DC, 24–25 April 2003; <http://www.paho.org/english/ad/dpc/vp/rimsa13-18-e.pdf>
6. Germanier, R. and Fürer, E., *J. Infect. Dis.*, 1975, **131**, 553–558.
7. Wahdan, M. H., Serie, C., Cerisier, Y., Sallam, S. and Germanier, R., *J. Infect. Dis.*, 1982, **145**, 292–295.
8. Edelman, R. and Levine, M. M., *Rev. Infect. Dis.*, 1986, **8**, 329–349.
9. Cabello, F., Agüero, M. E. and Fernandez, M. E., *Rev. Med. Chil.*, 1984, **33**, 488–490.
10. Hirschel, B., Wuthrich, R., Somaini, B. and Steffen, R., *Eur J. Clin. Microbiol.*, 1985, **4**, 295–298.
11. Baker, S. *et al.*, *J. Clin. Microbiol.*, 2005, **43**, 4418–4425.
12. Threlfall, E. J., *FEMS Microbiol. Rev.*, 2002, **26**, 141–148.
13. DeRoeck, D., Jodar, L. and Clemens, J., *N. Engl. J. Med.*, 2007, **13**, 1069–1071.
14. Eswarappa, S. M., Panguluri, K. K., Hensel, M. and Chakravorty, D., *Microbiology*, 2008, **154**, 666–678.
15. Lahiri, A., Das, P. and Chakravorty, D., *Microbiology*, 2008, **154**, 2837–2846.
16. Chakravorty, D., Hansen-Wester, I. and Hensel, M., *J. Exp. Med.*, 2002, **6**, 1155–1166.
17. Das, P., Lahiri, A., Lahiri, Ay. and Chakravorty, D., *Microbiology*, 2009, **155**, 2476–2489.
18. Cheminay, C., Möhlenbrink, A. and Hensel, M., *J. Immunol.*, 2005, **174**, 2892–2899.
19. van Velkinburgh, J. C. and Gunn, J. S., *Infect. Immun.*, 1999, **67**, 1614–1622.
20. Beier, D. and Gross, R., *Curr. Opin. Microbiol.*, 2006, **9**, 143–152.
21. Fluit, A. C., *FEMS Immunol. Med. Microbiol.*, 2005, **43**, 1–11.
22. McClelland, M. *et al.*, *Nature*, 2001, **413**, 852–856.
23. Ochiai R. L. *et al.* *Clin. Infect. Dis.*, 2007, **15**, S34–S38.
24. Salmonella typhi Vi O-Acetyl Pectin-rEPA Conjugate Vaccine; <http://clinicaltrials.gov/ct2/show/NCT00277147>
25. Tacket, C. O. *et al.*, *Infect. Immun.*, 2000, **68**, 1196–1201.
26. Negi, V. D., Singhamahapatra, S. and Chakravorty, D., *Vaccine*, 2007, **25**, 5315–5323.

ACKNOWLEDGEMENT. I thank Prof. M. S. Shaile for her critical suggestions during the preparation of this manuscript.

---

*Dipshikha Chakravorty is in the Centre for Infectious Disease Research, Department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore 560 012, India.*  
*e-mail: dipa@mcbl.iisc.ernet.in*