Immunity to Salmonella Infections

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1. INTRODUCTION

Immunity to typhoid fever has been of interest since the turn of the century, principally because of a desire to develop optimal vaccines for use by military personnel. The British were the first to try vaccination under the direction of Wright and Semple in 1897. The United States Army adopted compulsory vaccination in 1911, using the British method, which involved three injections of heat-killed organisms, spaced 1 week apart. The results were a stunning success, with the number of cases falling from over 350/100,000 to less than 25/100,000 once compulsory vaccination was instituted. At that time the causative organism was designated as Eberthella typhosa, the name being changed later to Salmonella typhosa, and finally to Salmonella typhi. Initially, the major antigens on the organism were determined to be the O (somatic antigens) and the H antigens (flagellar). In 1934 the Vi capsular antigen was discovered by Felix and Pitt and shown to be a major virulence factor of S. typhi. Considerable research was invested in trying to assess the relative contribution of the O and Vi antigens to the protection conferred by vaccination. Since the Vi antigen was preserved better by alcohol than by heat, alcohol-preserved whole-cell vaccines were also tested. In 1953 Landy introduced acetone-killed and dried cells. These various whole killed-cell formulations were compared in extensive double-blind field trials carried...
out in the late 1950s and 1960s in British Guyana, Yugoslavia, Poland, and Russia under the auspices of the World Health Organization (WHO).\(^{(5,6)}\) It was found that many of these nonviable preparations conferred high levels of relatively long-lasting protection (at least 7 years) on vaccinees.\(^{(7)}\) Thus, vaccines consisting of \(10^9\) whole killed cells have consistently demonstrated protection in humans against typhoid fever.

However, attempts to understand the antigens involved in the protection yielded data that were confusing. One approach was to correlate levels of antibody titers to the \(O\), \(H\), and \(Vi\) antigens induced by the various vaccine preparations with protective potency. Although poor correlations were found between protection and anti-\(O\) or anti-\(Vi\) titers, it should be appreciated that the antibody assays were agglutination tests which only measured IgM.\(^{(4)}\) A second approach was to try to assess vaccine potency with the capacity of vaccines to immunize and protect mice from challenge with \(S.\ typhi\) or with their ability to induce immune serum that would passively protect naive animals. Twenty laboratories in twelve countries engaged in these tests. A lack of concordance in the findings between laboratories emerged, with no clear correlations between vaccine efficacy in field trials and in laboratory tests in animals.\(^{(8)}\) Nonetheless, the field trial data showed that the heat-killed phenol-preserved vaccine and the acetone-killed vaccine were highly efficacious, and they have been used not only by the military, but also for vaccination of civilians in typhoid-endemic areas. However, all parenteral whole killed-cell vaccines have a major drawback in that they have considerable toxicity. Their endotoxin content causes reactogenicity, which includes systemic symptoms, such as fever and chills, and local symptoms, including pain, erythema, and swelling at the injection site. These problems with nonviable vaccines provided a major impetus for development of alternative vaccination strategies, which will be discussed in detail later in this chapter. One of these approaches is the use of live attenuated Salmonella as vaccines. Various mutants or genetically engineered strains have been tested and found to be efficacious. Studies in mice using these organisms, as well as sublethal doses of virulent Salmonella, have been instrumental in formulation of hypotheses regarding mechanisms of immunity to Salmonella.

2. ANIMAL MODELS

Vaccine potency testing for the WHO trials was carried out in mice that were challenged with \(S.\ typhi\) that had been coated with hog gastric mucin. In the absence of mucin, this organism was not virulent for mice, requiring greater than \(10^7\) organisms to achieve an \(LD_{50}\). An alternative mouse model,