Vaccine attributable severe dengue among Dengvaxia recipients in the Philippines.

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In 2016, WHO recommended that Dengvaxia, the first dengue vaccine, licensed for use in those aged 9 years or above, be considered for use in highly endemic regions where at least 70% of 9-year old children had been previously infected with dengue. The Philippines was the first country to introduce Dengvaxia on a large scale, in selected highly endemic regions targeting about 1 million children aged 9-10 years. In November 2017, Sanofi Pasteur reported an excess risk of hospitalized and severe dengue in vaccinees who had not had a previous dengue infection at the time of vaccination, based on retrospective analyses of data from the Dengvaxia Phase 3 trials, using a novel NS1 based antibody assay.[1] Following this report, the Philippine Dengvaxia programme was suspended. By then, over 830, 000 children had received at least 1 out of 3 recommended Dengvaxia doses. The news about the safety concerns in dengue naive vaccinees led to a major public outcry, with loss in vaccine confidence that extended to routine childhood vaccines.[2]

Parents whose children had received Dengvaxia were understandably alarmed by the reported adverse effect of the vaccine, as most parents will not have known whether or not their child had had a previous dengue infection, and any cases of severe dengue in vaccinees may have been attributed to the vaccine. Similarly, clinicians looking after vaccinated children admitted with severe dengue will also be tempted to attribute that episode to vaccine-enhanced disease. In reality, however, a minority of cases may be so attributable.

No vaccine is 100% efficacious and cases of breakthrough disease arise through vaccine failure. For the first licensed dengue vaccine, the issues of efficacy and safety are complex as both are driven by serostatus. Serostatus refers to whether a person had a previous dengue infection; seropositive persons had at least one dengue infections in the past, whereas seronegative persons are dengue-naïve. The efficacy of Dengvaxia against severe dengue in seropositive vaccinees in the Phase 3 trials was 84% (95% CI 63% to 93%).[1] The vast majority, possibly around 85%, of all vaccinees in the Philippines programme were likely seropositive.[3] Hence, we would expect to see breakthrough disease in seropositive vaccinees when exposed to natural infection, especially in light of the current outbreak of dengue in the Philippines. Cases of severe dengue following vaccination would be a mixture of breakthrough disease in seropositive vaccinees and enhanced disease in seronegative children.

It is important that the risks associated with Dengvaxia are put in an appropriate perspective. Firstly, many cases of hospitalised and severe dengue following vaccination are likely to be attributable to vaccine breakthrough cases in seropositive vaccinees, as a high proportion of vaccinees are likely to have been dengue seropositive, among whom the vaccine protects but does not give total protection. Secondly, among all children vaccinated, the overall incidence of hospitalised dengue is likely to be substantially lower in the 5 years following vaccination than would have been the case had no one been vaccinated.[4] On a population level, in highly endemic regions like those vaccinated in the Philippines, the number of dengue cases averted by the Dengvaxia substantially outweigh the number of vaccine-induced cases, and there is an overall net benefit to the population. Of course, vaccinating only those testing seropositive would be the preferred strategy for future use of the vaccine, but this depends on the development of sensitive and specific rapid point-of-care tests to identify this group.[5]

References

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