to a fatal outcome in the mother or stillbirth, abortion, or low-birth weight (LBW) babies. A study from rural Madhya Pradesh estimates that per year there were 220 000 women with malaria in pregnancy, 95 800 lost foetuses and 1000 died. According to the strategic plan for malaria control in 2007–12 in India, there is scope for introduction of chemoprophylaxis in pregnancy in areas with a high burden of malaria in pregnancy. However, this would require an estimation of the true burden of disease in these areas and a documentation of the safety and benefits of ITP in Indian settings.

REFERENCES


An effective dengue vaccine: A glass half full or half empty?

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SUMMARY

This study was a randomized, controlled, single-centre phase 2b trial of the efficacy of an investigational dengue vaccine, CYD-TDV. This is a recombinant, live-attenuated, tetravalent dengue vaccine (TDV). It is based on the yellow fever 17D vaccine strain, produced using Vero cells.

The study was conducted in the Muang district of Ratchaburi province of Thailand. This site was found suitable for the trial during an epidemiological study done earlier. Four thousand and two healthy schoolchildren aged 4–11 years were recruited from 35 schools. Those with an acute febrile illness or an immunodeficiency disease were excluded. Children were randomly assigned to receive either three doses of the dengue vaccine (n=2669) or a saline placebo (n=1333) subcutaneously at months 0, 6 and 12. The first 50 children randomized to the placebo arm received one dose of the rabies vaccine as placebo. However, the use of rabies vaccine in the placebo arm was stopped following the advice of the independent data monitoring committee.

All children were followed up for at least 13 months after the third dose of injection. Acute febrile illnesses were detected using school records, phone calls and home visits. In case of a febrile illness, parents were asked to take their child to the Ratchaburi Regional Hospital. Paired serum samples were collected at presentation and 7–14 days later. Acute samples were screened at a central laboratory. Virologically confirmed dengue was defined as a positive dengue serotype-specific polymerase chain reaction (PCR) or detection of NS1 dengue antigen by enzyme-linked immunosorbent assay (ELISA). Serious adverse effects were monitored until the sixth month after the last injection. Dengue immune responses were assessed in the first 300 enrolled children using sera collected at enrolment, and before and 4 weeks after each injection. Neutralizing antibody titres against each dengue serotype were also assessed.

Of the 4002 children enrolled over a period of one year, 3839 (96%) received three injections and 3673 (2452 in the vaccine group and 1221 in the placebo group) were included in the per-protocol analysis. At baseline, over 90% of the 300 children tested for immunogenicity were seropositive against dengue virus (DENV) or
Japanese encephalitis virus. Of the 2266 febrile episodes detected, there were 134 children (76 in the vaccine group and 58 in the placebo group) who had virologically confirmed DENV infection. Of these, 77 occurred more than 4 weeks after the third injection; 45 over 2522 person-years at risk in the vaccine group and 32 over 1251 person-years at risk in the placebo group. This gave a vaccine efficacy of 30.2% (95% CI –13.4% to 56.6%). Efficacy after at least one injection was 61.2%, 81.9% and 90% against DENV1, 3 and 4, respectively (all statistically significant). However, against DENV2, which accounted for 59% of all dengue episodes, it was 3.5% (95% CI –59.8% to 40.5%).

Serious adverse effects occurred at similar rates in the two groups. There were five episodes of severe dengue, three in the vaccine group and two in the placebo group. There were no dengue-related deaths. Dengue antibody titres rose significantly after each injection in the children tested for immunogenicity.

COMMENT

Dengue is a flavivirus that causes an estimated 50 million infections annually with 500 000 cases of dengue haemorrhagic fever and 22 000 deaths.1 While effective vaccines are available against other flaviviruses such as the Japanese encephalitis virus and the yellow fever virus, no effective vaccine is available against dengue.

Since there is no specific treatment available for dengue, preventive efforts have largely focused on vector control, an expensive strategy with low effectiveness. This has made the need for a vaccine all the more pressing. Although several candidate vaccines have emerged, no dengue vaccine has been licensed for clinical use.

Currently, two promising vaccines are undergoing clinical trials. The first is the vaccine named CYD-TDV which was tested in the present trial. This vaccine has been developed by researchers at Mahidol University, Thailand in partnership with Sanofi Pasteur, the vaccine division of Sanofi, a French pharmaceutical firm. It is a recombinant, chimeric, live-attenuated, tetravalent vaccine that combines a yellow fever strain 17D backbone with viral antigens from each of the four DENV serotypes. Details of vaccine structure and development have been published earlier by the research team.2

The safety and immunogenicity of this vaccine were shown to be acceptable in an earlier phase 2 trial in 1199 individuals aged 2–45 years in Singapore.3 Another CYD-TDV trial in Peru, which included 199 children, showed a robust immune response with seroconversion to all four DENV serotypes in 94% of vaccinees.4

Given the encouraging results from these studies, the results of the present phase 2b trial by Sabcharoen et al. were eagerly awaited. The trial was well planned; the field area had been surveyed beforehand for suitability. It was performed in an area endemic for DENV with circulation of all four serotypes. The authors adhered to the WHO guidelines for the clinical evaluation of dengue vaccines in endemic areas.5 The sample size was adequate. All three doses of vaccine were given to 96% of participants and 92% were included in the per-protocol analysis. All children were closely followed and febrile episodes evaluated and managed at a central hospital facility. Follow-up for adverse effects lasted more than a year after the last injection. A subset of vaccinees was evaluated for antibody titres to the vaccine strains and acute reactions to the injections were carefully monitored.

The authors found that vaccination led to significant efficacy against DENV1, 3 and 4. However, although a good immune response was generated, efficacy was lacking against DENV2, which accounted for 59% of all virologically confirmed dengue episodes. This outcome came as a surprise given the 60%–90% efficacy against the other three strains. The authors hypothesized that an antigenic mismatch between the CYD2 vaccine virus and the DENV2 virus could explain this failure.

Despite this disappointment, there is much that has been achieved by this trial. The authors have shown that a TDV can be safely given to a large cohort of children with a low incidence of immediate and delayed adverse effects. Excellent immunogenicity was found against all four strains of DENV. Concerns have been raised regarding the safety and efficacy of using a TDV in populations which have acquired antibodies to one or more flaviviruses, including DENV, as a result of previous infections. These have been laid to rest following this trial.

The antibody-dependent enhancement theory holds that pre-existing, non-protective, sub-neutralizing antibody from a prior infection with a DENV type enhances viral replication during infection with a different strain.5,6 Through enhanced release of cytokines, this results in severe forms of dengue infection.7 The same phenomenon was predicted to occur following vaccination. This has been a major barrier to vaccine development. However, the present trial produced evidence against this theory. Breakthrough cases following vaccination were not associated with greater disease severity.

A slightly different approach has been used by a team at the Walter Reed Army Institute of Research, USA in collaboration with GlaxoSmithKline Biologicals to create another candidate dengue vaccine. This vaccine uses all four strains of DENV which have been attenuated by serial passage in a primary dog kidney (PDK) cell line. It has been shown to be safe and effective in a recent phase 2 trial with an immune response of 66.7% after two subcutaneous injections given 6 months apart.8

Relevance in the Indian context

India is endemic for dengue infection with repeated epidemics akin to the one in New Delhi in 1996, affecting 10 000 people.9 These outbreaks lead to high morbidity, panic among the population and severe stress on healthcare facilities. Vector control measures have largely been unsuccessful in controlling dengue. An effective and safe vaccine would be of help in combating this disease.

This trial by the Mahidol University group is a step forward in the development of a dengue vaccine. The partial failure of the vaccine against DENV2 should be seen as a temporary setback to be overcome by further research.

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Road traffic noise: A risk factor for myocardial infarction?

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SUMMARY
A population-based cohort study was done to establish an association between road traffic noise and incident myocardial infarction (MI). The study was based on a Diet, Cancer and Health cohort. The cohort comprised 57 053 residents of Copenhagen and Aarhus, Denmark who were aged 50–64 years. Of these, 566 and 900 residents were excluded due to the presence of cancer and coronary artery disease, respectively. After further excluding persons with incomplete residential address and missing data on covariates, a total of 50 614 participants were studied. The enrolment was done from 1993 to 1997. Baseline characteristics such as sex, smoking status, smoking duration, smoking intensity, intake of fruit, vegetables and alcohol, body mass index, physical activity, calendar year, education, railway and airport noise, air pollution, baseline diastolic and systolic blood pressure, total cholesterol and self-reported diabetes were assessed at the time of enrolment and considered as potential confounders. The average follow-up period was 9.8 years.

Exposure to road traffic noise, for all present and historical residential cohort members who lived between 1988 and event/censoring, was calculated for the years 1990, 1995, 2000 and 2005. The road traffic noise was calculated by the Nordic prediction method as the equivalent continuous A-weighted sound pressure level (L$_{Aeq}$.). ‘A-weighting’ is a widely used scale to measure sound pressure levels, which correlates with the subjective response of the auditory system. It was expressed as L$_{Aeq}$—a composite index of noise exposure during day (L$_{da}$), evening (L$_{le}$) and night (L$_{ln}$). The exposure to railway noise from 1993–2000 was calculated by the same method. The information available from local authorities about noise zones (5 dB categories) was used to determine the noise impact from airports and airfields. The concentration of oxides of nitrogen (NO$_x$) in the air for each year (1988–2006) at each address was calculated by the Danish AirGIS modelling system.

The outcome was either incident MI (ICD 10: 121.0–121.9) identified from the Danish National Hospital Delivery and Danish Causes of Death Registry, or sudden cardiac death caused by an MI (ICD 10: 146.0–146.9) after validation by medical records. Cases with MI were ascertained from a review of the medical records from baseline through 2003, and as a diagnosed case from ward thereafter. Fatal MI was diagnosed as death within 30 days of diagnosis.

Left truncation at age of enrolment and right censoring at the age of MI (event), death, emigration or end of follow-up, whichever came first, was done. Left truncation means that the individuals who already had the event, viz. MI, were not included in the study. Right censoring means that there were individuals in whom the event did not occur till the end of the follow-up period of the study. The Cox proportional hazards model with age as the underlying time was used for analysis. The exposure to road traffic noise and NO$_x$ at a given age were calculated as time-weighted averages for the preceding 5 years (considering all present and historical addresses in that period) or as yearly exposure at the residence. Time-weighted averages were used to estimate a person’s daily exposure to road traffic noise and NO$_x$ taking into account the average levels of noise and NO$_x$ time spent in each area. To establish the association between MI and road traffic noise, incidence rate ratios (IRRs) were calculated for yearly road traffic noise at diagnosis, and time-weighted mean road traffic noise for 5 years preceding diagnosis. The association between exposure to road traffic noise and incident MI was estimated after adjusting for confounders stated earlier.

There was a strong positive correlation ($R_{Spearman}$=0.96, p=0.0001) between the distribution of road traffic noise exposure (L$_{Aeq}$) at the enrolment address and the time-weighted 5-year mean L$_{Aeq}$ preceding enrolment (considering historical addresses). The L$_{Aeq}$ and NO$_x$ in the study period ($R_{Spearman}$=0.62, p=0.0001) were also significantly correlated.

High risk for MI was associated with higher level of road traffic noise in a linear dose-response manner. Every 10 dB increase in road traffic noise led to a 12% higher risk for MI. For cases with fatal MI, the IRR per 10 dB yearly increase in road traffic noise was 1.25 (95% CI 1.07–1.46) which reduced to 1.17 (95% CI 0.96–1.43) after adjustment for confounders. There was no significant effect modification present between road traffic noise and incident MI across the strata of exposure variables such as age, sex, smoking status, years of education and exposure to railway noise.

The authors concluded that residential exposure to road traffic noise was positively associated with a risk for MI in a linear dose-response manner.