Research letters

Impact of immunisation on pertussis transmission in England and Wales

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Pertussis immunisation reduces disease frequency, but is not thought to prevent transmission. We show that vaccination has substantially reduced transmission in England and Wales.

Instances of symptomless pertussis reinfection are well documented,[1,2] so there is a clear distinction between the control of pertussis transmission and the prevention of disease. We have analysed high-resolution pertussis notification data to assess the consequences of vaccination for transmission. Our investigation of the impact of vaccination is based on changes in mean incidence and the pattern of epidemics.

Mass vaccination has led to a large decrease in reported cases of whooping cough in England and Wales.[3] This decrease represents an important achievement but we cannot assume that the associated infectious agents are circulating less in the population. Specifically, the vaccine may not prevent mild or symptomless infections, which are unlikely to be reported as cases of disease. Such subclinical infections may maintain the chain of transmission and prevent eradication of pertussis. Cherry[1] commented that "circulation of *Bordetella pertussis* cannot be controlled by our present pediatric immunisation program".

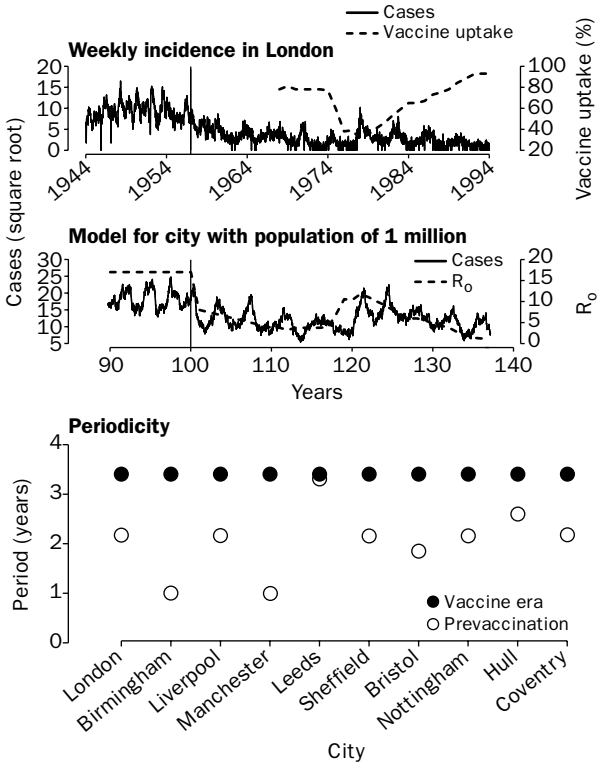

Figure 1: **Derivation of periodicities**
Top=weekly pertussis in London and estimated vaccine uptake. Middle=model incidence data for a city with a population of one million; the effective R_0 (number of secondary cases per primary case) shows a substantial drop in the vaccine era.[5] Bottom=the main periodicities in the ten largest cities in England and Wales.

The effectiveness of immunisation schemes can also be assessed through the relative changes in the interepidemic period after mass immunisation. Analysis of simple models indicates that a fall in transmission should be accompanied by an increase in the interepidemic period.[3] However, studies by Fine and Clarkson[4] suggested that vaccination had little effect on the interepidemic interval of pertussis in England and Wales, and that pertussis transmission had not been substantially affected by vaccination.[1,4] Their study is the source of the widespread belief that although pertussis vaccination prevents the onset of disease, it fails to control transmission or prevalence effectively.

We now have access to a much more extensive dataset (both temporally and spatially) than was available to Fine and Clarkson.[4] We found that the onset of pertussis vaccination coincided with a significant increase in the interepidemic interval, from 2·0–2·5 to nearly 4 years in the ten largest cities of England and Wales (figure 1). We argue that this dynamic shift indicates a substantial drop in transmission of the infectious agent; this conclusion is supported by a simple stochastic model, which captures the qualitative dynamics of whooping-cough epidemics (figure 1).[5] This finding implies a substantial decrease in the effective reproductive ratio of infection,[3] which in turn

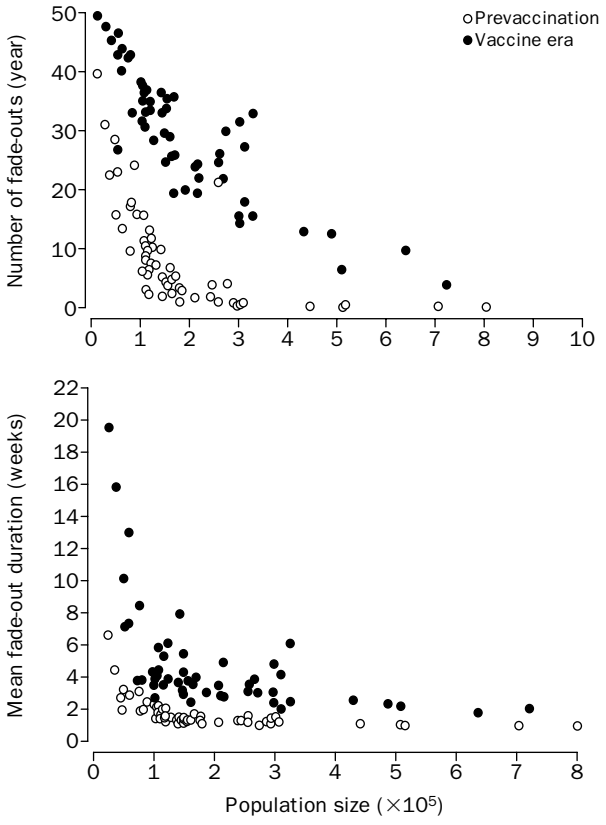

Figure 2: **Mean number and duration of fade-outs**

implies a substantial reduction in pertussis transmission in England and Wales. More complex pertussis models that incorporate different levels of immunity and age-specific vaccination schedules give qualitatively similar results.

In addition to the interepidemic interval, we explored other dynamic consequences of vaccination. The onset of mass vaccination coincided with a major change in the spatiotemporal patterns of pertussis incidence.[5] Vaccination was associated with a transition from spatially incoherent epidemics in the 1950s to geographically synchronised outbreaks in 1960s and 1970s with an almost 4-year period. Models support the hypothesis that this transition was caused by a substantial fall in transmission.[5]

Finally, we investigated the efficacy of vaccination by studying the pattern of fade-outs—ie, the frequency and duration of reports of no cases in individual locations (figure 2).[3] A very large increase in both number and duration of fade-outs occurred in the vaccine era, consistent with spatial synchronisation of epidemic troughs.[5] The importance of these observed changes in the fade-out structure very much depends on the frequency of mild or subclinical infections. In the absence of unequivocal evidence that the occurrence of symptomless infections radically increased after vaccination, the striking changes strongly indicate that vaccination has successfully reduced pertussis transmission.

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Autoimmune T cells as potential neuroprotective therapy for spinal cord injury

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Autoimmune T cells against central nervous system myelin associated peptide reduce the spread of damage and promote recovery in injured rat spinal cord, findings that might lead to neuroprotective cell therapy without risk of autoimmune disease.

Secondary degeneration after spinal cord injury can cause disability beyond the severity of the primary insult. We have shown[1] that autoimmune T cells specific to myelin basic protein (MBP) of the central nervous system (CNS) can enhance the recovery of an experimentally crushed optic nerve.

We investigated the role of autoimmune T cells in the treatment of experimentally crushed rat spinal cords.

18 rats were deeply anaesthetised, laminectomised, and had their spinal cords at T7–T8 contused by a weight drop device.[2,3] Six of the rats were then injected intraperitoneally with 10^7 anti-MBP T cells, six with 10^7 cells directed against the non-self antigen ovalbumin (OVA), and six with phosphate buffered saline (PBS). All the rats were paralysed immediately after the contusion (figure 1), but recovery began earlier in the rats treated with the anti-MBP T cells and, at all times from 11 days on, the anti-MBP T cell-treated group showed significantly greater locomotor recovery than did the controls. The mean maximum behavioural scores at plateau (1 month) were 1·5 (SE 0·8) for the PBS-treated group, 2·1 (0·2) for the anti-OVA T cell-treated control, and 7·7 (1·4) for the anti-MBP T cell-treated group (figure 1). Clinically, these scores showed an almost total lack of spontaneous motor activity in the controls, whereas the rats treated with the anti-MBP T cells could move all their joints and some could support their weight.

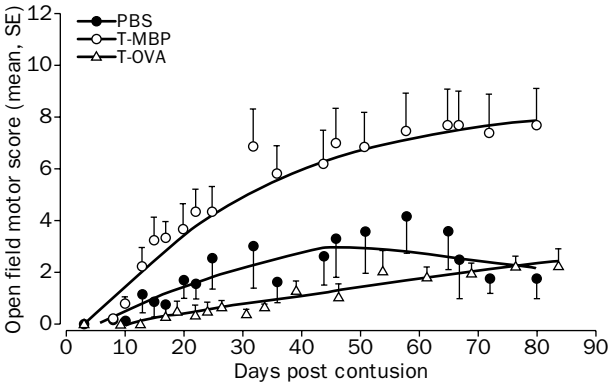

Figure 1: **Anti-MBP T cells enhance recovery of spontaneous motor activity after spinal cord contusion**
Following contusion and treatment with either cells or vehicle functional recovery over time was scored in an open field test on a scale of 0 (complete paralysis) to 21 (complete mobility)[2] by observers blinded to the treatment received by each rat. Mean values for each group (vertical bars SE) are shown. Differences between the group treated with the anti-MBP T cells and the other two groups, tested by repeated ANOVA, were significant ($p<0·05$).

The amount and integrity of the neural tissues remaining in control and treated rats were assessed by diffusion weighted magnetic resonance imaging (MRI). Spinal cords of rats were excised 2 months after trauma and treatment and were immediately fixed and placed in MRI tubes. Nine axial slices, positioned around the site of lesion, were subjected to diffusion weighted multislice spin echo imaging (Nevo U, Hauben U, Yoles E, et al, unpublished data). The accumulated diffusion anisotropy in each slice (SAI) was calculated, and in each rat, the slice with the lowest SAI was defined as the lesion site. The maps demonstrate preservation of longitudinally ordered tissue at the lesion site of the anti-MBP T cell-treated rats. The loss of tissue at the site of injury in the control rat is much greater than that seen in rats from the anti-MBP T-cell treated group.

Images of axial slices from the spinal cords of rats who received anti-MBP T cells, by contrast with the controls, showed areas of diffusion anisotropy along the entire length of the cord and a continuous longitudinal structure (figure 2). The accumulated values of diffusion anisotropy at the centre of the site of injury (where diffusion anisotropy was at its lowest) in the anti-MBP treated group was two-fold higher than in the controls. The neuroprotective effect of the autoimmune T cells was further substantiated by immunohistochemical analyses using confocal microscopy; the anti-MBP T cell-treated rats showed well-organised spared neural tissue with few if any cysts, whereas the control rats showed a gap in continuity of the neural tissue and large cysts (Hauben E, Butovsky O, Nevo U, et al, unpublished data).