

Bracho et al 2010 Large-scale application of highly-diluted bact for Lepto epidemic control

A review by Dr Martin Whitehead MRCVS

Bracho, G., Varela, E., Fernandez, R., Ordaz, B., Marzoa, N., Menendez, J., Garcia, L., Gilling, E., Leyva, R., Rufin, R., de la Torre, R., Solis, R.L., Batista, N., Borrero R. and Campa, C., (2010) Large-scale application of highly-diluted bacteria for Leptospirosis epidemic control *Homeopathy* Vol. 99 pp. 156-166

Summary

Within three neighbouring provinces of Cuba, the incidence of leptospirosis increased over 2005-2007, leading up to a major outbreak of the disease in the last quarter of 2007. In addition to the conventional public-health and medical response to the outbreak, 96% of the entire population (2,404,787) of the three affected provinces were treated with a leptospirosis nosode (a homeopathic 'vaccine'). Within a couple of weeks of starting the nosode administration campaign the outbreak resolved, with the number of cases returning to historical baseline levels. The authors interpret this coincidence in timing as proof that the nosode was highly effective at protecting against leptospirosis. However, even leaving aside the extreme implausibility of the nosode (which consisted of water with no *Leptospira* content and no other medical content) having any such effect, there are; (i) a major artefact introduced by the data collection which complicates data interpretation over the time of the nosode administration, (ii) no randomised control group to allow inference of causation from the coincidence in timing noted, and (iii) another much more plausible cause of the resolution of the outbreak relative to the timing of the nosode administration. Thus, this study does not support the authors' conclusion that the nosode was protective against leptospirosis.

Details of the study

The nosode

The nosode was made from inactivated bacteria of four *Leptospira* strains (as such, the intervention is strictly isopathic, not homeopathic). The bacteria were diluted 1-in-100 serially 200 times using standard homeopathic methods. At this level of dilution there is no chance that any of the initial leptospiral content of the 'mother tincture' remained in the nosode, which therefore consisted of either water or, possibly, a mix of water and ethanol (it is not stated which).

Five drops of the nosode is administered sublingually to each person twice, 7-9 days apart. The administration campaign started in week 45. It is not stated precisely how long it took the 5000 public-health personnel involved to administer the nosode twice to each of the well-over 2 million people treated but in the legend of Fig. 2 it states that coverage was 70% by week 48 and 92% at week 50.

The populations studied

The three affected provinces (popn. 2,404,787) are named the 'intervention region' (IR). The authors compare the week-by-week time course of leptospirosis incidence in the IR over 2007 and 2008 to that in the IR averaged over 2000-2006, and also to the time course of leptospirosis incidence in the whole of the rest of Cuba (popn. 8,834,547) in 2007 and 2008. They refer to the rest of Cuba as the 'control region' (CR). Note that the study is a cohort study and the population of the CR was not a 'control group' in the sense that would be used in a clinical trial because they did not experience the leptospirosis outbreak and were based in a different geographical region where factors relevant to leptospirosis incidence may be different to those in the IR. Nevertheless, the population of the CR provides some indication of what leptospirosis incidence in the IR might have been in the absence of the leptospirosis outbreak.

The data presented as supporting the effectiveness of the nosode

The only data relevant to any effect of the nosode is presented in Fig. 2B (all other data presented are from the CR and/or are historical). The raw data is leptospirosis incidence – number of cases per 100,000 people per week – in the IR week-by-week over 2007 and 2008. In 2007, from weeks 1-40 the incidence fluctuates from 1 to about 12 cases per 100,000 per week, mostly being low in that range up to week 20 and mostly being high in that range from weeks 20-40. After week 40, weekly incidence increases dramatically

reaching a maximum of 38 cases per 100,000 in week 46. The leptospirosis administration campaign began in week 45. By week 47 there had been a dramatic decline in incidence that continued such that by week 49, and until week 52, leptospirosis incidence was back down to about 3-4 cases per 100,000 per week, i.e., similar to incidence over the first quarter of 2007, before the outbreak.

In 2008, leptospirosis incidence was low all year, averaging about 2.5 cases per 100,000 per week.

Taken uncritically, the data in Fig. 2B, showing that leptospirosis incidence declined dramatically with two weeks of starting the nosode administration campaign, could indicate that the nosode was highly effective. Such a conclusion is highly implausible because the nosode did not contain any possible vaccinal or medicinal ingredient. However, leaving aside the issue of plausibility, there are three flaws in the study that confound any attempt to determine whether or not the nosode had any effect.

Flaw 1: Cuba's public health data-collection system introduced a major artefact into the annual pattern of incidence of leptospirosis

The data presented in the study was taken from the National Surveillance Program for zoonotic diseases run by Cuba's Ministry of Public Health. Local hospitals, polyclinics and doctor's clinics submit patient data and blood samples from suspicious cases to their Municipal or Provincial Centre for Hygiene and Epidemiology (PCHE), which has the appropriate laboratory facilities for diagnosis. Each PCHE generates a weekly report that is fed to the Ministry of Public Health, which release a national weekly report.

It is clear from the historical data presented in the paper that this system introduces a major artefact into the annual pattern of leptospirosis incidence. Fig. 1 of Bracho et al shows weekly median incidence of leptospirosis for the years 1990-2006 for the whole of Cuba (although not stated, the data in Fig. 1 appear to be total cases, not cases per 100,000 population). The median incidence in weeks 1 and 2 is about 1 case per week, and increases gradually to about 10 cases per week by week 6, and thereafter fluctuates only slightly to week 42 after which there is a marked increase up to week 52. Notably, week 52 itself has far more cases (median of about 100 cases) than any other week of the year (the next highest weekly incidence is about 38 cases). Astonishingly, after week 52, with a peak median incidence of 100 cases, in week 1, as already noted, the median incidence is only 1 case. This temporal pattern of disease incidence is biologically completely implausible.

No infectious disease could possibly follow such a time course. It is not possible from the paper to determine what causes this artefact in apparent seasonal incidence, but it can be speculated that there is some time delay in reporting of cases from the bottom to the top of the surveillance network, and that bureaucratic and/or regulatory factors require reporting of cases occurring in a year to be reported in that year. Such a speculation could account for the remarkably low incidence in the first few week of the year, the increase in the last 10 or so weeks of the year, with the very large increase in week 52.

From Fig. 3, this annual increase over the last few weeks of the year was present in the CR in years 2000-2006 (median data) and in each of 2007 and 2008.

From Fig 2, the annual increase over the last few weeks of the year was present in the IR in years 2000-2006 (median data). However, it was not present in either 2007 or 2008. It is not clear why this end-of-year increase in incidence was not present at the end of 2007 or 2008. Bracho et al's interpretation is that the nosode (which was re-applied in 2008 a year after the 2007 application) prevented this increase. An alternative interpretation is that the increasing level of leptospirosis in the IR in the years 2005 to 2007, and the major outbreak in 2007, triggered an improvement in the speed of data reporting – i.e., that the seasonal pattern of incidence reported was more accurate in 2007 and 2008 in the IR than it had been historically, or than in the CR. However, this cannot be ascertained from the paper.

I note that the artefact is largest in the last few weeks of the year, i.e., the period shortly after the administration of the nosode in 2007. While there is no way of knowing whether or not the weekly pattern of incidence in the IR in 2007 shown in Fig. 2B is accurate or not, the presence of this very large artefact in the CR data in 2007, and in the historical data from both the IR and CR, casts doubt on the reliability of the weekly incidence data in the last few weeks of 2007, i.e., in precisely those few weeks during and immediately after the nosode administration campaign.

The large artefact present in the historical data from the IR and the CR, and in the CR data in 2007 and 2008, make meaningful comparisons of the pattern of weekly incidence between the IR data in 2007 and 2008 to either historical data or CR data meaningless. Much of Bracho et al's Results and Discussion sections consist of such comparisons.

Flaw 2: There was no control group, randomisation or blinding.

Despite the flaw in data collection that means that it is not known how accurate the pattern of leptospirosis incidence by week is over the last several weeks of 2007, i.e., over the time during and just after the nosode administration campaign, there is no doubt that there was a major leptospirosis outbreak that resolved towards the end of 2007, i.e., around the time of the nosode administration campaign, at which time leptospirosis incidence appears to have returned to historical background levels.

However, correlation does not prove causation, and so some other factor(s) than the nosode may have brought the leptospirosis outbreak to an end. This is particularly relevant because there was also a conventional public-health and medical response to the outbreak. In the absence of a randomised (untreated, placebo-controlled or positive-controlled) control group among the population affected by the leptospirosis outbreak, it is impossible to know what proportion of resolution of the outbreak, if any, can be attributed to the nosode.

Moreover, the opposite of blinding applied in that both the population and the medical profession were very actively informed about this treatment: The nosode was administered by 5,000 personnel of the public health system, including family doctors, nurses, social workers and paramedics. Each person treated was verbally informed about the treatment and consent obtained. In addition, information about the product and homeopathic intervention were provided by local TV, radio programs, newspapers and by free information desks spread over the IR, but not over the CR.

Flaw 3: There was a conventional public-health and medical response to the leptospirosis outbreak as well as the nosode administration campaign.

The healthcare personnel and the public in the IR were intensively targeted with information about the increase of leptospirosis and about the homeopathic intervention. Other control measures including sanitation, vector control, education, chemoprophylaxis (doxycycline) and conventional vaccination against leptospirosis were used at the time of the outbreak. Presumably, increased effort was applied to these other measures in the IR at the same time that the homeopathic intervention was applied, although this is not specifically stated in the paper.

96% of the IR population were treated with the nosode. In comparison, conventional vaccination or chemoprophylaxis (using doxycycline) was given to only 3% of the population in the IR (i.e., to approximately 72,000 people). Although this number seems small in comparison, it should be noted that even at its highest (in 2007), the annual incidence of leptospirosis in the IR was 'only' 16.7 per 100,000 of population (=0.0167%), i.e., approximately 402 people over the entire IR in the year. Thus, vaccination and chemoprophylaxis, although very limited compared to the homeopathic intervention, was still applied to 180 times more people than were identified as infected with leptospirosis. As stated in the Methods section, "individuals within risk groups were vaccinated when identified" with a conventional vaccine, and doxycycline chemoprophylaxis "was applied mainly for focal treatment and outbreak control to high-risk groups when identified". Such conventional public-health and medical procedures can be very effective in dealing with outbreaks of leptospirosis, thereby providing a highly plausible explanation for the resolution of the outbreak in the IR in 2007.

In week 42 of 2008, there was a localised outbreak of leptospirosis (>100 cases) in a closed population in the CR, as shown in Fig. 3. Bracho et al state that only conventional measures and no homeopathic measures were applied in the CR, and this outbreak was "quickly controlled by chemoprophylaxis". Clearly, the conventional measures used in Cuba were highly effective. In the Discussion it is stated "the coverage of conventional measurement of control including vaccination and chemoprophylaxis was similar in both [IR and CR] regions since their applications followed the current guidelines from the Ministry of Public Health of Cuba."

Martin Whitehead, BSc, PhD. BVSc, CertSAM, MRCVS

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