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Whole-cell inactivated Leptospirosis vaccine

Future prospects

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Leptospirosis is an infectious disease of worldwide distribution that is caused by pathogenic spirochete bacteria of the genus *Leptospira*. It is transmitted by the urine of an infected animal and contagious in a moist environment. Epidemiological studies indicate that infection is commonly associated with certain occupational workers such as farmers, sewage workers, veterinarians, and animal handlers. The annual incidence is estimated at 0.1–1 per 100,000 in temperate climates to 10–100 per 100,000 in the humid tropics. A disease incidence of more than 100 per 100,000 is encountered during outbreaks and in high-exposure risk groups. The 11 countries in South-East Asia (SEA) together have a population of more than 1.7 billion and a work force of about 770 million with more than 450 million people engaged in agriculture. Because of the large number of serovars and infection sources and the wide differences in conditions of transmission, the control of leptospirosis is complicated and will depend on local conditions. The available leptospirosis vaccines are mono- or polyvalent cellular suspensions. These cells are inactivated by chemical agents like formaldehyde and phenol, or by physical agents like heat. The vaccine confers protection for not longer than about one year, while there are cases that need revaccination six months later during epidemic periods.

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Leptospirosis is an infectious disease of worldwide distribution that is caused by pathogenic spirochete bacteria of the genus *Leptospira* called spirochetes. Leptospirosis is an emerging zoonotic disease of public health importance in countries of the World Health Organization's SEA Region. It is transmitted by the urine of an infected animal and is contagious in a moist environment. Although rats, mice and other rodents are important primary hosts, a wide range of other mammals including dogs, deer, rabbits, cattle, buffaloes, sheep, and pigs also carry and transmit the disease as secondary hosts. Humans get infected through skin contact with water or soil-containing urine from infected animals or from consuming contaminated food or water.[1] Person-to-person transmission is extremely rare since man is a dead-end host for leptospiral dissemination. In contrast, leptospires can survive for long periods in the renal tubules of infected animals without causing illness. Most human infections occur in young adult men and children and result from occupational or environmental exposure.[2]

Epidemiological studies indicate that infection is commonly associated with certain occupational workers such as farmers, sewage workers, veterinarians, and animal handlers. Leptospirosis can also be transmitted during recreational activities such as picnicking, hiking, swimming and canoeing.[3-5] Prevalence rates increase with age[6,7] probably due to a higher chance of exposure. Males have been shown to have a higher chance of contracting the disease than females, suggesting a strong occupational component in transmission.[6] Leptospires can survive in untreated water for months or years, but cannot survive desiccation or salt water. Leptospirosis is still widely overlooked and underreported, mainly because the

clinical features are non-specific, with signs and symptoms similar to those seen in many other infectious diseases such as influenza-like illness, headache, muscle and abdominal pain.[8] Furthermore, confirmation of leptospirosis requires a Microscopic Agglutination Test (MAT), which is not always available, and rapid diagnostic tests are not reliable.

The annual incidence of leptospirosis is estimated at 0.1–1 per 100,000 in temperate climates to 10–100 per 100,000 in the humid tropics. A disease incidence of more than 100 per 100,000 is encountered during outbreaks and in high-exposure risk groups.[9] Most countries in SEA are endemic for leptospirosis. The incidence of leptospirosis is often influenced by various socio-cultural, occupational, behavioral and environmental factors. The risk is higher in rural areas where animals are present in large numbers and the population is mainly involved in agriculture or animal husbandry.[10] The 11 countries in the SEA region together have a population of over 1.7 billion and a work force of about 770 million with more than 450 million people engaged in agriculture. Seasonal outbreaks have been reported in northern Thailand and Gujarat state of India following heavy rainfall and flooding. Major outbreaks in SEA were reported due to a cyclone in Orrisa (1999), flooding in Jakarta (2002), and in Mumbai (2005) and Sri Lanka (2008). Leptospirosis is a possible cause of acute pyrexia of unknown origin (PUO) after flooding, and most PUO cases are not further investigated,[10] hence further contributing to underreporting of disease.

Leptospirosis has been a significant problem in low-lying areas of India that are densely populated and prone to flooding and water stagnation during monsoon. The outbreaks of leptospirosis are increasingly being reported from Kerala, Gujarat, Tamil Nadu and Karnataka.[11] But with better facilities to detect the disease, the disease now is being reported from almost all parts of India.[12-15]

Multi-centric investigations in India indicate that leptospirosis account for about 13% of cases of acute febrile illness reporting to the hospitals.[16] Besides, leptospirosis is the cause of a significant proportion of cases of non-hepatitis A and E jaundice, non-malarial febrile illnesses, and non-dengue hemorrhagic fever in SEA.[17]

Because of the large number of serovars and infection sources and the wide differences in conditions of transmission, control of leptospirosis is complicated and depends on local conditions. Control of disease can be achieved by controlling the reservoir or reducing infection in animal reservoir populations such as dogs or livestock, but control of wild animals may be difficult. Preventive measures must be based on knowledge of the groups at particular risk of infection and local epidemiological factors.

Prevention and control should be targeted at:[18]

I. Source of infection;

II. Route of transmission between the source and the human host; or

III. Infection or disease in the human host.

It is important to establish which animal species are the infection sources in a particular area.

Control measures to be targeted to the local reservoir species of animals include:

- Reduction of certain animal reservoir populations, e.g., rats.
- Separation of animal reservoirs from human habitations by means of fences and screens.
- Immunization of dogs and livestock.
- Removal of rubbish and maintenance of cleanliness around human habitations.
- Encouraging people not to leave food around, especially in recreational areas where rats may be present.
- Leptospira vaccine to prevent disease; however, serovar specificity limits the efficacy of killed whole-cell vaccines.

Killed Whole-Cell Leptospiral Vaccine

The mono- or polyvalent cellular vaccines for leptospirosis are available in many countries, and have concentrations per dose of 100–500x10^6 cells per serovar. The cells are inactivated by chemical agents like formaldehyde and phenol, or physical agents like heat. Doses are injected subcutaneously (SC) or intramuscularly (IM) with a 7- to 21-d interval. Only one vaccine is available globally, SPIROLEPT manufactured by Sanofi-Pasteur for SC injection as two doses of 1 mL each at a 15-d interval, with the third dose 4–6 mo after the first dose, followed by biannual revaccination. The MAT titers after vaccination are significantly lower than those developed after natural infection, and seroconversion was of low frequency (about 20–60%).[19-22] However, protection has been reported to be high in such populations, and efficacy rates of such vaccines have been 60–100%.[23-25]

The vax-SPIRAL vaccine was developed in Cuba for at-risk populations. Vaccine efficacy is 78% (95% confidence interval: 59–88%); side effects are general discomfort and mild pain at the injection site. This trivalent vaccine contains a whole-cell suspension of *L. interrogans* including serogroups *Canicola serovar canicola*, *Icterohemorragiae serovar copenhageni* and *Pomona serovar mozdok*, inactivated with formaldehyde, adsorbed onto aluminum hydroxide, with 0.01% thimerosal as preservative.[25] Vaccination is deeply IM in the deltoid, with two 0.5 mL doses administered in a 6-week interval.[26] Vaccine-induced protection is for no longer than about one year, while there are cases that need revaccination after only six months during epidemic periods. It is also known that induced immunity is serovar-specific, although it is possible to a lesser degree to detect protection in serovars of the same serogroup as well as in different serogroups.

Side effects of whole-cell vaccines have been reported to include systemic and local reactions at various frequencies. To reduce side effects ascribable to serum in cultures, a vaccine that consisted of leptospires grown in protein-free medium has been developed.

There is a report on an outer envelope vaccine, which has been evaluated in China and shown to induce good protection with fewer side effects and higher agglutinating titers than those for whole-cell vaccine. Vaccination using the outer envelope vaccine also reduced the number of patients with vaccine-unrelated serogroup strains.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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