

## Can vaccinating sheep reduce the occurrence of caseous lymphadenitis?

A Knowledge Summary by

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## KNOWLEDGE SUMMARY

### PICO question

Is there a decrease of caseous lymphadenitis in vaccinated sheep compared to unvaccinated sheep?

### Clinical bottom line

The evidence provided by the studies used is strong (all have been randomised controlled trials), supporting the hypothesis that sheep vaccinated against caseous lymphadenitis (CLA) are less likely to develop the disease when compared to unvaccinated sheep. Vaccination may be a useful tool in the prevention and control of clinical CLA following a risk assessment.

### Clinical Scenario

Caseous lymphadenitis (CLA) is an important clinical disease found mainly in sheep which can have a high economic impact on sheep production. Knowing this, a sheep breeder asks the veterinarian during a regular visit to his farm how he could avoid this disease in his flock. He knows there are vaccines on the market, but wonders if they are really effective.

### The evidence

In all the studies the animals were randomly allocated to experimental treatment groups, which provides a higher degree of confidence in the study (although most studies did not detail how this randomisation was done). From a total of 238 studies found, 218 were excluded. Of these, 169 were not related to the PICO question, 30 were not primary studies, three were excluded due to being written in a foreign language, 12 were related to other species and four were not available. Of the 20 studies selected, 10 had to be excluded because they were duplicates. In all the studies used it was found that animals vaccinated against CLA are less likely to acquire the disease when compared to unvaccinated animals. The vaccination for CLA is an effective measure for prophylaxis of the disease, since vaccinated animals were significantly less affected by the disease when compared to unvaccinated animals.

### Summary of the evidence

Sohier et al. (2018)	
<b>Population:</b>	From a group of 50 lambs negative for CLA (determined by enzyme-linked immunosorbent assay (ELISA) test), a total of 15 Balady ewes, approximately 8–10 months old, participated.
<b>Sample size:</b>	15 sheep (three per group)
<b>Intervention details:</b>	15 were allotted at random to five groups each group consisting of three animals. Four groups were vaccinated by four different vaccine formulas, and the fifth group was kept as an unvaccinated control

	<p>group.</p> <p><b>Group A (vaccine 1):</b> Toxoid phospholipase D (PLD) – a preparation of culture filtrate from isolated <i>Corynebacterium pseudotuberculosis</i> biovar 1. 1 ml of the filtrate was mixed with 1 ml of oil adjuvant vaccine, dose (2 ml) contained 23 µg PLD, and the vaccine was inoculated subcutaneously, in the middle third of the neck.</p> <p><b>Group B (vaccine 2):</b> PLD – bacterin composed of formalin-killed <i>C. pseudotuberculosis</i> whole cells mixed with the toxoid PLD vaccine. 164 killed bacteria cells and 23 µg PLD/1 ml, and the dose (2 ml) was inoculated subcutaneously, in the middle third of the neck.</p> <p><b>Group C (vaccine 3):</b> Toxoid PLD with covaccine 8 – covaccine 8 is an imported vaccine formulated from a mixture of clostridial toxins, obtained from Schering Plough Animal Health. The mixture contained 23 µg PLD in 40 ml of covaccine 8, 2 ml inoculated subcutaneously, in the middle third of the neck.</p> <p><b>Group D (vaccine 4):</b> Toxoid PLD vaccine combined with the polyvalent clostridial vaccine – <i>Clostridium perfringens</i>, <i>Clostridium tetani</i>, <i>Clostridium septicum</i>, <i>Clostridium chauvoei</i>, and <i>Clostridium novyi</i>. 40 ml of polyvalent clostridial vaccine mixed with 6 g lyophilised powder formulated culture filtrate PLD. The polyvalent is a local vaccine prepared by Veterinary Serum and Vaccine Research Institute (Abbasia, Cairo, Egypt). The 2 ml dose of the vaccine was inoculated subcutaneously in the middle third of the neck.</p> <p><b>Group E (control):</b> Unvaccinated animals.</p> <p>All the vaccinated animals were revaccinated after 3 weeks of the first vaccination.</p> <p>After 3 weeks of the last vaccination, all five groups were challenged with virulent biovar 1 sheep origin isolate with 2 ml suspension containing 4×10<sup>6</sup> colony forming unit (CFU), 1 ml vaccine was inoculated subcutaneously in the middle third of the each side of the neck. The non-specific cellular immune response represented by stimulated macrophages was measured at 2 weeks after the challenge while the specific excited lymphocytes response was assessed at 4 weeks.</p> <p>Statistical analysis was done using model Generalised Linear Model (GLM) of Statistical Analysis System (SAS) and software version 6.12.</p>
<b>Study design:</b>	Randomised controlled trial
<b>Outcome studied:</b>	<p>Perform a comparative innate and acquired immune response assessment of four different vaccine formulas to evoke protection against induced CLA in sheep.</p> <p>The specific immune response was evaluated through lymphocyte proliferation assay using ELISA BrdU kit, while the non-specific</p>

	response was estimated by superoxide anion production and lysozyme activity assays.
<b>Main findings: (relevant to PICO question):</b>	The study indicated that the toxoid PLD vaccine alone (group A) was most efficient and provided innate and acquired immune response in animals against CLA. The vaccine evoked the highest stimulation index, which expressed specific lymphocyte proliferation response by a big margin compared to the other combined vaccines.
<b>Limitations:</b>	It does not inform whether the control animals were vaccinated with placebo and does not report the method of randomisation.

Eshra et al. (2018)	
<b>Population:</b>	15 native sheep, of about 6–8 months of age were apparently healthy with no history of CLA. They were kept under clinical observation for 1 month. All sheep selected for the experiment had negative ELISA test.
<b>Sample size:</b>	15 sheep (five per group)
<b>Intervention details:</b>	<p>Sheep were divided into three groups (five animals per group) as follows:</p> <p><b>Group I:</b> Vaccinated with 0.1 ml of Bacillus Calmette–Guérin (BCG) (supplied by Veterinary Serum and Vaccine Research Institute, used for vaccination of sheep dose of 0.1 ml), simultaneously injected intradermally with the first dose of 2.0 ml of the prepared CLA vaccine injected subcutaneously, then booster dose injected 21 days apart.</p> <p><b>Group II:</b> Vaccinated with 2.0 ml of prepared CLA vaccine then booster dose injected 21 days apart (injected subcutaneously).</p> <p><b>Group III:</b> Control group.</p>
<b>Study design:</b>	Randomised controlled trial.
<b>Outcome studied:</b>	<p>The study was directed to develop oil adjuvant vaccine from killed local isolated <i>C. pseudotuberculosis</i> field strain and evaluation of its humoral and cellular immunity response in sheep of the prepared vaccine only and combined with BCG.</p> <p>They were evaluated as cellular and humoral immune responses, through evaluation by phagocytic activity and index, and differential count of leukocytes and ELISA, respectively.</p>
<b>Main findings: (relevant to PICO question):</b>	<p>Proved (in groups I and II) to induce cellular and humoral immunity and could be used for prevention and control of CLA in sheep.</p> <p><b>Group I:</b> Immune response mediated by phagocytic activity and phagocytic index between 0 and 44 days average of 62.25%;</p> <p><b>Group II:</b> Immune response mediated by phagocytic activity and phagocytic index between 0 and 44 days average of 61%;</p>

	<p><b>Group III:</b> Immune response mediated by phagocytic activity and phagocytic index between 0 and 44 days average of 55.5%.</p> <p>Average humoral immune response (by optical density of colored reaction):</p> <p><b>Group I:</b> day 0: 0.136; day 21: 0.397; day 44: 0.394; day 60: 0.371;</p> <p><b>Group II:</b> day 0: 0.149; day 21: 0.372; day 44: 0.382; day 60: 0.332;</p> <p><b>Group II:</b> day 0: 0.143; day 21: 0.133; day 44: 0.145; day 60: 0.145.</p>
<b>Limitations:</b>	Does not explain how randomisation was performed and whether the control animals were vaccinated with placebo.

Ghani et al. (2016)	
<b>Population:</b>	Male lambs (Awassi), ages ranged 5–7 months old. The animals were bred in the Veterinary Medicine University of Baghdad. All lambs were treated by ivermectin 200 µg per kg of body weight subcutaneous at the rate of 1 ml per 50 kg as anthelmintic treatment for internal and external parasites before starting the experiment. Lambs divided into three groups each group consisted of five lambs.
<b>Sample size:</b>	15 lambs (five per group)
<b>Intervention details:</b>	The animals were separated into three groups. There is no information on how this allocation was made.  <b>Group I:</b> five lambs as negative control.  <b>Group II:</b> five lambs vaccinated (a commercial vaccine prepared by Colorado Serum Company (U.S.A.), detoxified and purified the whole culture of <i>C. pseudotuberculosis</i> contains thimerosal as preservative used in healthy sheep as a killed bacterin-toxoid vaccine. The vaccine injected subcutaneously in a dose of 2 ml in axillary space and repeated in four weeks in opposite axillary space).  <b>Group III:</b> five lambs as positive control.
<b>Study design:</b>	Randomised controlled trial
<b>Outcome studied:</b>	To know the efficacy of commercial vaccine (Case-Bac Vaccine) by immunisation trials against the CLA disease in sheep and study cellular and humoral immunity.  Humoral and cell mediated immune response was detected during the period of experiments, the temperature, pulse rate and

	<p>respiration rate were determined weekly.</p> <p>Cellular immune responses of the vaccinated and control groups were evaluated by delayed type of hypersensitivity (DTH) skin test.</p>
<p><b>Main findings: (relevant to PICO question):</b></p>	<p>The vaccine appeared to offer an excellent protection against the development of CLA in sheep and the vaccine could play an important role in the control of the disease in infected sheep flocks.</p> <p>Antibody titer two weeks after first vaccination dose (mean optical density values):</p> <p><b>Group I:</b> 0.096 ± 0.013</p> <p><b>Group II:</b> 0.426 ± 0.26 – The maximum titre was reached in the eighth week after vaccination (1.984 ± 0.776) and then the antibody titers begun to decrease to 0.95 ± 0.446</p> <p><b>Group III:</b> 0.093 ± 0.01</p>
<p><b>Limitations:</b></p>	<p>Does not state the method of randomisation.</p>

Izgür et al. (2010)	
<p><b>Population:</b></p>	<p>Mixed Akkaraman lambs, approximately 6 months old</p>
<p><b>Sample size:</b></p>	<p>140 lambs</p>
<p><b>Intervention details:</b></p>	<p>140 lambs were selected, of these 28 were positive for <i>C. tuberculosis</i> and were excluded from the studies. Of the 112 lambs negative for antibodies against the exotoxin of <i>C. pseudotuberculosis</i> as determined by the haemolysis inhibition test (HIT), 90 animals were randomly chosen. 90 lambs were allotted at random to three groups (30 lambs in each group):</p> <p><b>Group I:</b> was vaccinated with a vaccine prepared from <i>C. pseudotuberculosis</i> PI 18 strain. The vaccine injected subcutaneously in a dose of 0.5 ml (two doses).</p> <p><b>Group II:</b> with a vaccine prepared from <i>C. pseudotuberculosis</i> Cy 5 strain. The vaccine injected subcutaneously in a dose of 0.5 ml (two doses).</p> <p><b>Group III:</b> was used as a control and was subcutaneously injected with 2.0 ml phosphate buffer solution (PBS).</p>
<p><b>Study design:</b></p>	<p>Randomised controlled trial</p>
<p><b>Outcome studied:</b></p>	<p>Identify major antigens of <i>C. pseudotuberculosis</i> isolated from different sheep flocks in Turkey and to evaluate the efficacy of the vaccine formulated as bacterin + toxoid + Freund's complete adjuvant (FCA) (groups I and II) against bacterial challenge in lambs. Cellular immune responses of the vaccinated and control groups</p>

	were evaluated by DTH skin test.
<b>Main findings: (relevant to PICO question):</b>	When a local <i>C. pseudotuberculosis</i> (PI 18) strain was used and formulated as per ml of the vaccine, 1.5x10 <sup>8</sup> colony-forming unit (CFU) of <i>C. pseudotuberculosis</i> bacterin + toxoid + 1/2 FCA of the toxoid, obtained a high percentage of protection regarding the potential of this vaccine to control CLA in sheep, as seen in groups I and II.
<b>Limitations:</b>	Method of randomisation not stated and not all animals present at the beginning of the study were allocated to the groups.

Stanford et al. (1998)	
<b>Population:</b>	1992: 620 lambs (Rambouillet, Suffolk, Finn, Dorset and Romanov) 1993: 453 lambs (Rambouillet, Suffolk, Dorset, Romanov and Finn) 1994–1996: nine flocks containing 2176 ewes and lambs (not informed breeds) Serum samples were collected prior to vaccination from all animals (mature stock and lambs). The microagglutination test was used to distinguish among vaccinated and unvaccinated animals.
<b>Sample size:</b>	3249 lambs
<b>Intervention details:</b>	In 1992, lambs were assigned to one of 3 groups: <b>Group I:</b> control (no vaccine); <b>Group II:</b> whole cells (WC) + 2-acetamido-2-deoxy-3-O-D-2-propionyl-L-alanyl-D-isoglutamine-D-glucopyranose-snglyceryl-dipalmitoyl (MDP-GDP), administered intramuscularly; <b>Group III:</b> Glanvac, administered subcutaneously;  In 1993, lambs were randomly assigned to one of 3 groups: <b>Group I:</b> control (no vaccine); <b>Group II:</b> WC+MDP-GDP, administered intramuscularly; <b>Group III:</b> Case-Vac, administered subcutaneously;  1994-1996, ewes and lambs were assigned to 2 groups: <b>Group I:</b> control (saline), administered subcutaneously; <b>Group II:</b> WC+MDP-GDP, administered intramuscularly; It does not report the number of animals allocated to each group and the dose of each injection.
<b>Study design:</b>	Randomised controlled trial
<b>Outcome studied:</b>	To assess the efficacy and impact of vaccination with two commercial (Glanvac-6 and Case-Vac) and one experimental (WC+MDP-GDP).  Identify major antigens of <i>C. pseudotuberculosis</i> isolated from different sheep flocks in Turkey and to evaluate the efficacy of the vaccine formulated as bacterin + toxoid + Freund's complete adjuvant (FCA) against bacterial challenge in lambs. Cellular immune responses of the vaccinated and control groups were evaluated by

	<p>DTH.</p> <p>Serum samples were collected prior to vaccination from all animals (mature stock and lambs) and 1, 3, 6, 9, and 12 months after vaccination.</p>
<p><b>Main findings: (relevant to PICO question):</b></p>	<p>When a local <i>C. pseudotuberculosis</i> (PI 18) strain was used and formulated as per ml of the vaccine, <math>1.5 \times 10^8</math> CFU of <i>C. pseudotuberculosis</i> bacterin + toxoid + 1/2 FCA of the toxoid, we obtained protection regarding the potential of this vaccine to control of CLA in sheep.</p> <p>In all industry flocks, antibody titres for both lambs and mature stock were significantly higher than those of controls immediately prior to, and 1 month after, the booster vaccination.</p>
<p><b>Limitations:</b></p>	<p>It does not report the doses of each vaccine type and how randomisation was performed.</p>

Panton et al. (1995)	
<p><b>Population:</b></p>	<p>5 month old lambs</p>
<p><b>Sample size:</b></p>	<p>450 lambs</p>
<p><b>Intervention details:</b></p>	<p>Three groups (150 lambs per group)</p> <p>In each group 50 lambs were artificially infected with <i>C. pseudotuberculosis</i> and 100 were uninfected, and were separated for 40 months. One lot of 50 infected lamb and 100 uninfected lambs were vaccinated against CLA.</p> <p>Four weeks after the second vaccination, 50 lambs from each group were artificially infected with <i>C. pseudotuberculosis</i> and run separately for a further 4 weeks.</p> <p>50 artificially infected lambs being run with 100 uninfected lambs.</p> <p>Serology was checked to verify seroconversion, by means of antibodies of <i>C. pseudotuberculosis</i> through ELISA.</p> <p>Differences in CLA infection rates and seroconversion rates between groups of lambs were analysed using chi-square. Analysis of differences in numbers of lesions was done by Kruskal-Wallis one way analysis of variance.</p> <p>In each group 50 lambs were vaccinated as indicated before artificial infection:</p> <p><b>Group I:</b> Vaccinated against CLA, enterotoxaemia and tetanus; percentage with lesions 4%.</p> <p><b>Group II:</b> Vaccinated against enterotoxaemia and tetanus; percentage with lesions 44%.</p> <p><b>Group III:</b> Vaccinated against enterotoxaemia and tetanus; percentage with lesions 48%.</p>



	<p>In each group 100 lambs were run with 50 artificially infected lambs:</p> <p><b>Group I:</b> Vaccinated against CLA, enterotoxaemia and tetanus; percentage with lesions 2%.</p> <p><b>Group II:</b> Vaccinated against CLA, enterotoxaemia and tetanus; percentage with lesions 20%.</p> <p><b>Group III:</b> Vaccinated against enterotoxaemia and tetanus; percentage with lesions 76%.</p>
<b>Study design:</b>	Randomised controlled trial
<b>Outcome studied:</b>	<p>Investigate the relative importance of different models of CLA and dissemination under conditions found incompatible within sheep flocks.</p> <p>Evaluated percentage of lambs with lesion CLA and number of lesions, besides the presence of antibodies to <i>C. pseudotuberculosis</i> exotoxin and cell wall.</p>
<b>Main findings: (relevant to PICO question):</b>	<p>Lambs vaccinated against CLA and naturally exposed to infection had 74% lower infection rate than unvaccinated sheep.</p> <p>Lambs vaccinated against CLA had a 97% lower infection rate (groups I and II).</p> <p>Unvaccinated lambs had a 76% infection rate (groups III).</p> <p>Vaccinated lambs infected with CLA have 96% fewer lung abscesses compared with unvaccinated infected lambs and therefore less likely to spread this disease to other lambs.</p>
<b>Limitations:</b>	Does not inform if vaccines have been administered intramuscularly or subcutaneously and how randomisation was performed.

Menzies et al. (1991)	
<b>Population:</b>	Female lambs and kids from one sheep flock. (The study was conducted parallel with goats and sheep. This Knowledge Summary only considers the results of the sheep).
<b>Sample size:</b>	88 lambs (44 controls and 44 vaccinates)
<b>Intervention details:</b>	<p><b>Group I:</b> Vaccinated; 44 lambs</p> <p><b>Groups II:</b> Unvaccinated; 44 lambs</p> <p>Females and offspring were allocated to groups.</p> <p>The animals were vaccinated between 2.5 and 3.5 months of age, the vaccination was repeated 1 month later and again 11 months later.</p> <p>Each dose of vaccine consisted of 0.25 ml sterile saline, 0.25 ml mineral oil with 3% Arlcel A and either 5.0 mg dried whole <i>C. pseudotuberculosis</i> cells (initial vaccination and 1 month booster) or 1.0 mg dried whole cells (12 month booster). The total volume for</p>

	<p>each injection was 0.5 ml.</p> <p>The serums were analysed by microagglutination assay for the detection of antibodies to <i>C. pseudotuberculosis</i>. Animals were monitored for the development of abscesses by the technician at each serum collection visit and by routine observation by the farm managers.</p> <p>The level of significance of the microagglutination was determined by the Student's t-test and was used the logrank test for difference in proportions of new cases in each group over time.</p>
<b>Study design:</b>	Randomised controlled trial
<b>Outcome studied:</b>	The purpose of this field trial was to evaluate the efficacy of a killed whole cell vaccine in preventing CLA in sheep by induction of infection.
<b>Main findings: (relevant to PICO question):</b>	<p>There was a significant difference in the proportion of vaccinated sheep that developed CLA compared to the control sheep at each time interval except less than 6 months post initial vaccination.</p> <p>The vaccine appeared to produce a persistently elevated serum antibody titre to <i>C. pseudotuberculosis</i> as measured by the microagglutination assay. There was also a statistically significant degree of protection in sheep against the development of clinical CLA.</p> <p>The vaccine could have a significant role in the control of CLA in infected sheep.</p>
<b>Limitations:</b>	It does not detail the populations or how the randomisation was performed and does not inform if vaccines have been administered intramuscularly or subcutaneously.

Eggleton et al. (1991)	
<b>Population:</b>	Romney Marsh lambs, 3–4 months of age
<b>Sample size:</b>	133 lambs
<b>Intervention details:</b>	<p>Lambs were vaccinated with two doses of vaccine (2.0 ml – interval of 28 days).</p> <p><b>Group 1</b> – immunised with monocomponent vaccine (vaccine prepared from <i>C. pseudotuberculosis</i>); 38 lambs; administered subcutaneously.</p> <p><b>Group 2</b> – immunised with the combined vaccine (vaccine prepared from <i>C. pseudotuberculosis</i> and <i>Clostridium perfringens D</i>, <i>Clostridium novyi B</i>, <i>Clostridium tetani</i>, <i>Clostridium septicum</i> and <i>Clostridium chavouei</i>); 38 lambs; administered subcutaneously.</p>

	<p><b>Group 3</b> – immunised with the combined vaccine (vaccine prepared from <i>C. pseudotuberculosis</i>, <i>Clostridium perfringens D</i>, <i>Clostridium novyi B</i>, <i>Clostridium tetani</i>, <i>Clostridium septicum</i> and <i>Clostridium chavouei</i> and selenium); 24 lambs; administered subcutaneously.</p> <p><b>Group 4</b> – control; 33 lambs</p> <p>Serology and necropsy were performed (to verify lesions caused by CLA).</p>
<b>Study design:</b>	Randomised controlled trial
<b>Outcome studied:</b>	Compare the protective efficacy of monocomponent and combined clostridial-corynebacterial vaccines.
<b>Main findings: (relevant to PICO question):</b>	<p>Regarding necropsy, 12/145 animals were omitted after accidental death. 17/33 animals belonging to the control group had lesions, as well as 4/38 animals from group 1, 3/38 animals from group 2, 2/24 from group 3.</p> <p>All three vaccines afforded an equal and high level of protection. 91% (91/100) of vaccinated sheep exhibiting no lesions of caseous lymphadenitis CLA, compared with 51.5% (17/33) affected sheep in the control group).</p> <p>Average lesion counts were 1.2 per affected vaccinated sheep and 4.5 per affected control sheep.</p> <p>Antitoxin responses to the clostridial toxoids incorporated in the combined vaccines were not affected by inclusion of the <i>C. pseudotuberculosis</i> toxoid or the sodium selenate.</p> <p>The results indicate the overall efficacy of vaccines in controlling CLA infection.</p>
<b>Limitations:</b>	It does not detail the populations or how the randomisation was performed and does not report whether placebo was used in the control group

Eggleton et al. (1991)	
<b>Population:</b>	Romney Marsh lambs, 6 months of age (maintained at the CSL Field Station (Woodend, Victoria, Australia).
<b>Sample size:</b>	84 (16 animals were omitted from the study because they died).
<b>Intervention details:</b>	<p>Each group started with 20 lambs, but 16 animals were omitted from the study because they died.</p> <p>Vaccine was prepared from <i>C. pseudotuberculosis</i> toxoid combined with aluminum hydroxide as adjuvant.</p> <p>Each sheep received two doses of 2 ml of the appropriate vaccine administered subcutaneously in the neck. The interval between doses was 34 days.</p>

	<p><b>Control group (unvaccinated):</b> 17 lambs of which 15 were affected by CLA.</p> <p><b>Group 1 (vaccine high toxine-toxoid: cell-free toxoid):</b> 14 lambs of which three were affected by CLA.</p> <p><b>Group 2 (vaccine high toxine-toxoid-cells: toxoid with formalin-killed cells):</b> 15 lambs of which four were affected by CLA.</p> <p><b>Group 3 (vaccine low toxine-toxoid: cell-free toxoid):</b> 18 lambs of which four were affected by CLA.</p> <p><b>Group 4 (vaccine low toxine-toxoid-cells: toxoid with formalin-killed cells):</b> 20 lambs of which five were affected by CLA.</p>
<b>Study design:</b>	Randomised controlled trial
<b>Outcome studied:</b>	Verify if there is adequate protection in sheep vaccinated against CLA.
<b>Main findings: (relevant to PICO question):</b>	<p>The primary responses and peak secondary responses to the four vaccines did not differ widely, and the subsequent decline of antitoxin titres with time was identical for vaccine groups 3 and 4, with only minor exception in the fourth vaccine group.</p> <p><b><u>Necropsy results:</u></b></p> <p><b>Control group (unvaccinated):</b> 15 (15/17) were affected. Ten sheep had lesions in both lung and carcass, 4 had lung lesions only and one had carcass lesions only. The average number of lesions per affected sheep was 27.1</p> <p><b>Group 1 – 3 (3/14)</b> were affected the lesions being found in the lungs only. The average number of lesions per affected sheep was 2.0.</p> <p><b>Group 2 – 4 (4/15)</b> were affected, all with carcass lesions only. The average number of lesions per affected sheep was 1.5</p> <p><b>Group 3 – 4 (4/18)</b> were affected, 3 with lung lesions only and one with kidney lesions only. The average number of lesions per affected sheep was 3.0.</p> <p><b>Group 4 – 5 (5/20)</b> were affected, one with carcass and lung lesions, 2 with carcass lesions only and 2 with lung lesions only. The average number of lesions per affected sheep was 3.6.</p> <p>The protective potency of the vaccines was not improved by the inclusion of cells of <i>C. pseudotuberculosis</i>.</p>
<b>Limitations:</b>	It does not detail how statistical analysis of the data was performed and population and method of randomisation is not stated.

<b>LeaMaster et al. (1987)</b>	
<b>Population:</b>	Romney Marsh lambs, 6 months of age
<b>Sample size:</b>	63 mixed-breed, white-faced lambs

<b>Intervention details:</b>	<p>Each group started with 21 lambs.</p> <p><b>Group 1:</b> was vaccinated of using 2 ml a <i>C. pseudotuberculosis</i> bacterin given subcutaneously in the right axillary region at the beginning of the study.</p> <p><b>Group 2:</b> was vaccinated twice, being the first vaccination done on the same day as the group 1 and the second 4 weeks after</p> <p><b>Group 3 (unvaccinated):</b> control group was given saline solution (2 ml subcutaneously).</p> <p>Blood samples were collected immediately prior to the first vaccination and then weekly until week 11. From week 11 to the end of the study (week 25), samples were collected approximately every 2 weeks.</p> <p>ELISA was used to detect antibodies against <i>C. pseudotuberculosis</i>.</p> <p>13 weeks after inoculation all lambs were necropsied without knowledge of treatment groups to verify the presence of abscesses.</p>
<b>Study design:</b>	Randomised controlled trial
<b>Outcome studied:</b>	To evaluate efficacy of a <i>C. pseudotuberculosis</i> bacterin to protect sheep immunologically against the development of CLA, through controlled challenge exposure experiments.
<b>Main findings: (relevant to PICO question):</b>	<p>The number of internal lesions per lamb was four for group 1, two for group 2, and 14 group for 3.</p> <p>The average number of abscesses per lamb was seven for group 1, four for group 2 and 32 for group 3.</p> <p>The results of the study indicated that the vaccine provided immunological protection of lamb against challenge exposure of <i>C. pseudotuberculosis</i>.</p>
<b>Limitations:</b>	It does not detail the populations or how the randomisation was performed.

## Appraisal, application and reflection

In the study by Stanford et al. (1998) three experiments were carried out in different periods, with a large population of 3249 lambs of different breeds. Commercial vaccines were used and one that had not been tested previously of whole cell containing the synthetic adjuvant muramyl dipeptide-sn-glyceridipalmitoyl (WC+MDP-GDP), and both were efficient in provoking immune response.

Panton et al. (1995) conducted an experiment with 450 lambs, where some animals were vaccinated and others were not and some periods were challenged with *C. pseudotuberculosis*. LeaMaster (1987) also conducted an experiment comparing vaccinated and unvaccinated animals, and one of the vaccinated groups received two doses of vaccine and demonstrated that vaccinated animals had fewer internal lesions and abscesses, especially those who received two doses of vaccine.

Eggleton (1991) conducted two studies, which found similar efficacy of all vaccines used, indicating the overall efficacy of vaccines in the control of CLA infection. Menzies et al. (1991) found a significant difference in the proportion of vaccinated sheep that developed CLA compared to control (unvaccinated) sheep at each

time interval, except less than 6 months after initial vaccination

Izgür et al. (2010) and Ghani et al. (2016) found encouraging results comparing vaccinated and unvaccinated animals, where again it was found that vaccinated animals are at a lower risk of contracting clinical disease. Eshra et al. (2018) demonstrated that the inactivated *C. pseudotuberculosis* vaccine prepared with adjuvant with the ISA 206 montanide oil associated with the BCG vaccine induced cellular and humoral immunity and could be used for prevention and control of CLA in sheep.

Syame et al. (2018) verified the efficacy of several vaccines including those combined and concluded that the PLD toxoid vaccine alone was more efficient and provided immune response in animals against CLA, causing a higher rate of stimulation, expressing a greater proliferative response than the other vaccines.

In conclusion, all studies are primary and performed through randomisation (having as a limitation that is not explained how the randomisations was performed). Nevertheless there is evidence that the vaccination is an efficient prophylactic measure against caseous lymphadenitis for sheep flocks.

## Methodology Section

Search	
Databases searched and dates covered:	CAB Abstracts on the OVID Platform 1973 – 2018 Week 51 PubMed accessed via the NCBI website 1910 – December 2018
Search strategy:	<p><b>CAB Abstracts</b></p> <ol style="list-style-type: none"> <li>(sheep or sheeps or ovine or ovines or ovis or lamb or lambs or ewe or ewes or ram or rams or dam or dams).mp. or exp sheep/ or exp ewe/ or exp dams/ or exp rams/ or exp ovis/</li> <li>(caseous lymphadenitis or CLA).mp. or exp caseous lymphadenitis/</li> <li>(vaccine or vaccines or vaccinate or vaccinated or vaccination or immunize or immunized or immunization or immunise or immunised or immunisation or inoculate or inoculated or inoculation).mp. or exp vaccines/ or exp immunization/ or exp inoculation</li> <li>1 and 2 and 3</li> </ol> <p><b>PubMed</b></p> <ol style="list-style-type: none"> <li>sheep or sheeps or ovine or ovines or ovis or lamb or lambs or ewe or ewes or ram or rams or dam or dams</li> <li>caseous lymphadenitis or CLA</li> <li>vaccine or vaccines or vaccinate or vaccinated or vaccination or immunize or immunized or immunization or immunise or immunized or immunisation or inoculate or inoculated or inoculation</li> <li>1 and 2 and 3</li> </ol>
Dates searches performed:	9 January 2019

## Exclusion / Inclusion Criteria

Exclusion:	Did not answer PICO question, non-primary research, not English or Spanish or Portuguese language, study in other species and was not possible to access the study.
Inclusion:	Answer PICO question, primary research, English or Spanish or Portuguese language, study in lambs and was possible to access the study.

Please add/delete rows as necessary

Search Outcome							
Database	Number of results	Excluded – did not answer PICO question	Excluded – non-primary research	Excluded – not English or Spanish or Portuguese language	Excluded – study in other species	Excluded - It was not possible to access the study	Total relevant papers
CAB Abstracts	160	108	27	3	9	4	9
PubMed	78	61	3	0	3	0	11
Total relevant papers when duplicates removed							10

## CONFLICT OF INTEREST

The author declares no conflict of interest.

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