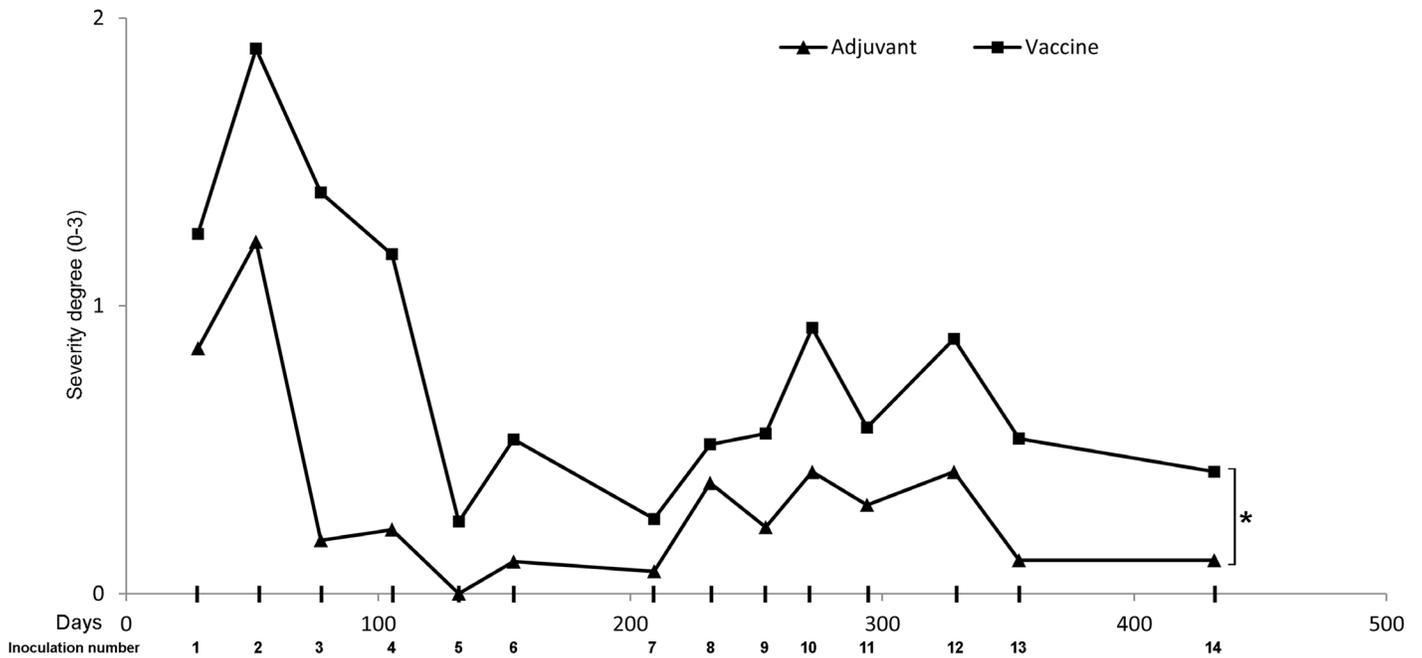


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**S1**

Supplemental Figure S1. Degree of severity of in vivo post-inoculation local reactions, evaluated by palpation. Each value is the mean of the degree of severity in the group at an evaluation date. Days: Days post first inoculation. Inoculation number: Sequential number of a given inoculation (Supplemental Table S2) \*P<.001. Mann Whitney's U test.

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**Supplemental Table S1.** Characteristics of the lambs and flocks used.

Flock	Breed	Geographic location	Management
1	Purebred <sup>a</sup>	Experimental farm <sup>c</sup> (University of Zaragoza)	Fully indoor; treatment groups not in contact
2	Crossbred <sup>b</sup>	River Valley <sup>d</sup>	Intensive <sup>g</sup>
3	Crossbred <sup>b</sup>	Pre-Pyrenees area <sup>e</sup>	Extensive <sup>g</sup>
4	Purebred <sup>a</sup>	River Valley <sup>f</sup>	Extensive <sup>g</sup>

<sup>a</sup>: Rasa Aragonesa breed

<sup>b</sup>: Commercial crosses of Rasa Aragonesa x Romanov

<sup>c</sup>: 41°41'N 0°52'W

<sup>d</sup>: 41°31'N 0°32'W

<sup>e</sup>: 42°9'N 0°12'W

<sup>f</sup>: 41°36'N 0°41'W

<sup>g</sup>: Treatment groups pooled together and mixed with the rest of the flock

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**Supplemental Table S2.** Description of the vaccines used. Aluminum content was established by inductively coupled plasma atomic emission spectrometry and calculated per total dose.

Vaccine number (Fig. 1)	Commercial name	Manufacturer	Antigen/s	Injection number (Fig. 1)	Injection flank		mg of Al per dose
					Right (n)	Left (n)	
1	Heptavac P Plus	MSD Animal Health S.L.	<i>Pasteurella multocida</i> , <i>Mannheimia haemolytica</i> , <i>Clostridium</i> spp.	1, 2, 9	2	1	7.5
2	Autogenous vaccine	Exopol	<i>Staphylococcus aureus</i> spp. <i>anaerobius</i>	3, 4, 14	3	NA	1.64
3	Vanguard R	Zoetis	Rabies virus	5	1	NA	1.03
4	Agalaxipra	Hipra	<i>Mycoplasma agalactiae</i>	6, 7	2	NA	6.76
5	Ovovac CS	Hipra	<i>Chlamydophila abortus</i> , <i>Salmonella abortus ovis</i>	8, 9	2	NA	5.60
6	Autogenous vaccine	Exopol	<i>Corynebacterium pseudotuberculosis</i>	10, 11	2	NA	1.32
7	Bluevac-1	CZ Veterinaria S.A.	Bluetongue virus serotype 1	12, 13	2	NA	4.18
8	Bluevac-4	CZ Veterinaria S.A.	Bluetongue virus serotype 4	12, 13	NA	2	4.16
9	Bluevac BTV 8	CZ Veterinaria S.A.	Bluetongue virus serotype 8	15, 16	2	NA	4.40

Abbreviations: NA: Not applicable

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**Supplemental Table S3.** Histopathological evaluation of the granulomas.

Granulomas	Scoring	Description
Voluminous macrophages	0 to 3	0: Absence 1: Less than 50 % of the cell population 2: 50 % to 75 % of the cell population 3: More than 75 % of the cell population
Multinucleated giant cells	P/A <sup>a</sup>	>3 nuclei giant cells, either foreign body or Langhans type
Lymphocytes	0 to 3	0: Absence 1: 1-2 inconspicuous groups 2: 3-4 readily visible groups 3: >4 voluminous groups
Tertiary lymphoid tissue	P/A	Group/s of densely packed lymphocytes with formation of germinal centers
Neutrophils	P/A	Group/s of >10 neutrophils
Necrosis	0 to 3	0: Absence 1: Slight multifocal eosinophilia 2: Central necrosis <50% of the section 3: Central necrosis >50% of the section
Mineralization	0 to 3	0: Absence 1: Rare, amorphous, multifocal <50 µm in diameter 2: Well-defined, crystalloid, coalescing areas 50-200 µm in diameter 3: Markedly crystalloid coalescing areas 200-500 µm in diameter
External fibrosis (capsule)	P/A	> 15 µm collagenous capsule
Internal fibrosis	P/A	Streams, bundles and trabeculae of fibrocytes, fibroblasts and collagen fibers
Internal hemorrhages	P/A	Aggregates of extravasated erythrocytes between macrophages
External hemorrhages	P/A	Aggregates of extravasated erythrocytes in the capsule and/or peripheral tissue
Internal blood vessels	P/A	Newly-formed blood vessels between macrophages
Eosinophilic crystalloid bodies	0 to 3	0: Absence 1: 1-4 bodies 2: 5-8 bodies 3: >9 bodies

<sup>a</sup>: P/A: Presence/Absence

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**Supplemental Table S4.** Histopathological evaluation of the right preescapular lymph nodes.

<b>Lymph nodes</b>	<b>Scoring</b>	<b>Description</b>
Cortical hyperplasia	0 to 3	0: Absence. 1: Mild increase in cortical thickness. Non-coalescing lymphoid follicles 2: Moderate increase in cortical thickness. Increased lymphoid follicles 3: Marked and diffuse increase in cortical thickness. Coalescing lymphoid follicles
Prominent germinal centers	0 to 3	0: Absence. 1: <50 % of follicles show germinal center 2: 50-75 % of follicles show germinal center 3: >75 % of follicles show a germinal center with increase in size
Aggregates of voluminous macrophages	P/A <sup>*</sup>	At least 4, 15-25 $\mu$ m macrophages with foamy to granulated cytoplasm

<sup>\*</sup>P/A: Presence/absence