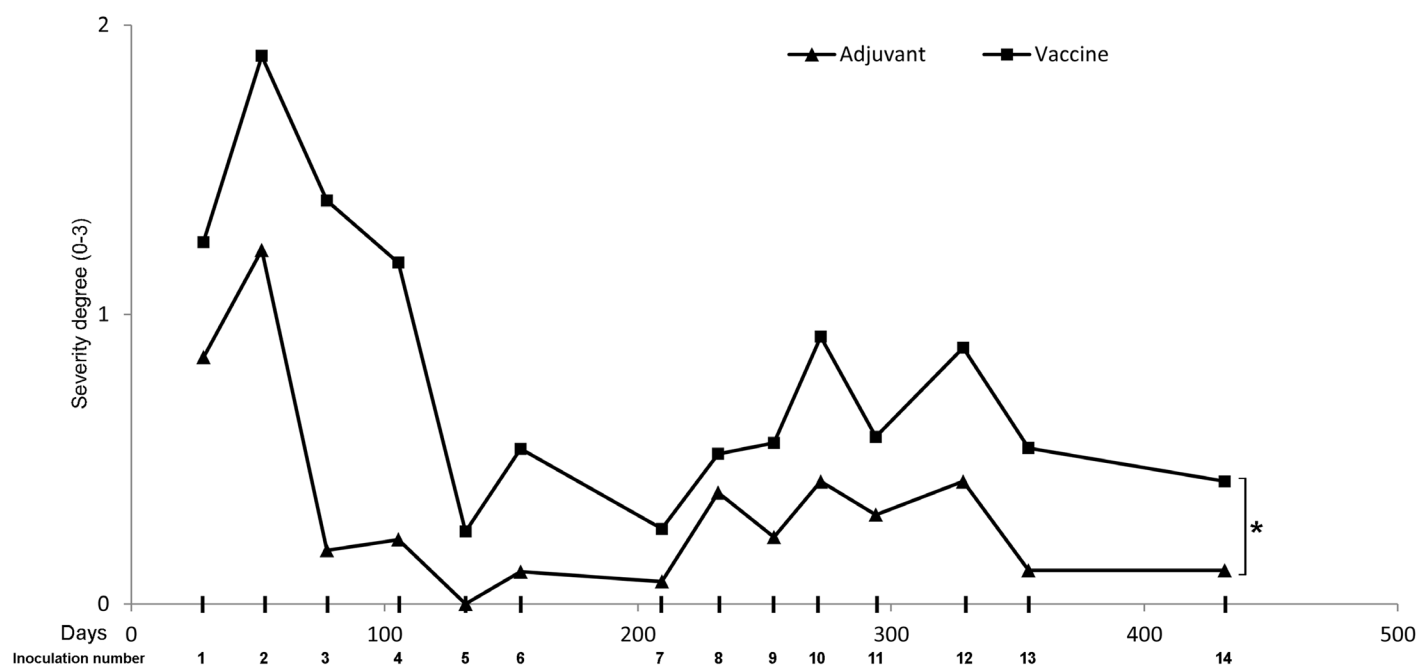


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S1

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 ^a	Experimental farm ^c (University of Zaragoza)	Fully indoor; treatment groups not in contact
2	Crossbred ^b	River Valley ^d	Intensive ^g
3	Crossbred ^b	Pre-Pyrenees area ^e	Extensive ^g
4	Purebred ^a	River Valley ^f	Extensive ^g

^a: Rasa Aragonesa breed

^b: Commercial crosses of Rasa Aragonesa x Romanov

^c: 41°41'N 0°52'W

^d: 41°31'N 0°32'W

^e: 42°9'N 0°12'W

^f: 41°36'N 0°41'W

^g: 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 ^a	>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

^a: P/A: Presence/Absence

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

Lymph nodes	Scoring	Description
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 [*]	At least 4, 15-25 µm macrophages with foamy to granulated cytoplasm

^{*} P/A: Presence/absence