## S1 Table. Characteristics of included studies.

No	Study	Sample size	Treatment	Intervention duration	Comparison groups	Outcome measure of interest	Effect sizes
Hum	an <i>in vivo</i> studi	ies	L				
1	de Kruif <i>et al.</i> (2007)	Human healthy male subjects	Administration with LPS (4 ng/kg)	1.5h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 1.42 (0.29, 2.95)
		(n=8)	, C - C,	4h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	TNF-α protein expression: 0.00 (-0.98, 0.98)
				24h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	TNF-α protein expression: 0.00 (-0.98, 0.98)
				3h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 1.21 (0.11, 2.30)
				4h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 1.25 (0.15, 2.35)
2	De Vox <i>et al.</i> (2009)	Human healthy male subjects	Administration with LPS (4 ng/kg)	1.5h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 1.51 (0.16, 2.86)
		(n=6)		4h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	TNF-α protein expression: 0.00 (-1.13, 1.13)
				1h-2h (1 <sup>st</sup> ), 24h (2 <sup>nd</sup> )	Group 1: Two- challenges Group 2: One-challenge	TNF-α protein expression	(Negative favours one-challenge) TNF-α protein expression: -0.25 (-1.38, 0.89)
						IL-6 protein expression	(Negative favours one-challenge) IL-6 protein expression: -0.35 (-1.50, 0.79)
3	Draisma <i>et al.</i> (2009)	Human healthy male subjects	Administration with LPS (2 ng/kg)	1.5h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 4.01 (2.65, 5.36)
		(n = 14)		4h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 0.00 (- 0.74, 0.74)
				1.5h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 2.97 (1.85, 4.09)

				4h  1h (1st), 2h (2nd)	Group 1: One-challenge Group 2: Control Group 1: Two- challenges Group 2: One-challenge	IL-6 protein expression  TNF-α protein expression  IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 0.88 (0.10, 1.66) (Negative favours one-challenge) TNF-α protein expression: -0.91 (- 1.69, -0.12) (Negative favours one-challenge) IL-6 protein expression: -2.29 (- 3.28, -1.31)
4	Grondman et al. (2019)	Human healthy male subjects (n = 15)	Administration with LPS (2 ng/kg) (1st); ex vivo monocytes stimulated with LPS (10 ng/ml) (2nd)	4h or 7d (1 <sup>st</sup> ); 24h (2 <sup>nd</sup> )	Group 1: Two-challenges Group 2: One-challenge	TNF-α protein expression  IL-6 protein expression	Not estimable  Not estimable
5	Hoogerwerf et al. (2008)	Human healthy male subjects (n = 8)	Bronchial instillation of LPS (4 ng/kg)	6h	Group 1: One-challenge Group 2: Control	IRAK3 mRNA expression	(Positive favours one-challenge) IRAK3 mRNA expression: 0.70 (-0.32, 1.72)
6	Koch et al. (2017)	Human healthy male subjects (n = 15)	Administration with LPS (2 ng/kg)	0, 1, 1.5, 2, 3, 4, 5, 6, 7, 8h	Group 1: One-challenge Group 2: Control	TNF-α protein expression IL-6 protein expression	Not estimable
7	Kox et al. (2011)	Human healthy male subjects (n = 12)	Administration with LPS (4 ng/kg)	1.5h 4h	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control	TNF-α protein expression TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 1.46 (0.54, 2.38) (Positive favours one-challenge) TNF-α protein expression: 2.79 (1.62, 3.97)
				1.5h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 2.06 (1.03, 3.08)
				4h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 0.73 (-0.10, 1.56)
				1.5h (1 <sup>st</sup> ), 1.5h (2 <sup>nd</sup> )	Group 1: Two-challenges	TNF-α protein expression	(Negative favours one-challenge)

			Administration with LPS (4 ng/kg)		Group 2: One-challenge	IL-6 protein expression	TNF-α protein expression: -0.94 (-1.79, -0.09) (Negative favours one-challenge) IL-6 protein expression: -1.18 (-2.06, 0.20)
8	Lankelma et al. (2017)	Human healthy male subjects	Administration with LPS (4 ng/kg)	1.5h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	2.06, -0.30)  (Positive favours one-challenge)  TNF-α protein expression: 0.70 (-0.32, 1.72)
		(n = 8)	ng/kg/	4h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	TNF-α protein expression: 0.00 (-0.98, 0.98)
				2h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 0.90 (-0.14, 1.95)
				4h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 0.77 (-0.25, 1.80)
9	Leentjens et	Human	Administration	0, 2, 4, 6, 8,	Group 1: One-challenge	TNF-α protein expression	Not estimable
	al. (2012)	healthy male	with LPS (2	24h	Group 2: Control	IL-6 protein expression	
		subjects	ng/kg)	0, 2, 4, 6, 8,	Group 1: Two-	TNF-α protein expression	Not estimable
		(n = 6)		24h (1 <sup>st</sup> ); 0,	challenges	IL-6 protein expression	
				2, 4, 6, 8, 24h (2 <sup>nd</sup> )	Group 2: One-challenge		
10	Leijte <i>et al</i> . (2018)	Human healthy male subjects (n = 10)	Administration with LPS	2.5h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 5.30 (3.27, 7.33) (Positive favours one-challenge)
		(		4h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	TNF-α protein expression: 2.96 (1.62, 4.31) (Positive favours one-challenge)
				2.5h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	IL-6 protein expression: 1.86 (0.83, 2.90) (Positive favours one-challenge)
				4h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	IL-6 protein expression: 1.40 (0.40, 2.41) (Negative favours one-challenge)
				2.5h (1 <sup>st</sup> ), 3h (2 <sup>nd</sup> )	Group 1: Two-challenges	TNF-α protein expression	TNF-α protein expression: -1.24 (-2.21, -0.26)
					Group 2: One-challenge	IL-6 protein expression	(Negative favours one-challenge)

Peters van (2021)   Pet								IL-6 protein expression: -1.51 (-
Ton et al. (2021)  Realthy male subjects (n = 5)  Ton et al. (2021)  Realthy male subjects (n = 5)  Ton et al. (2021)  Realthy male subjects (n = 5)  Ton et al. (2021)  Realthy male subjects (n = 5)  Ton et al. (2021)  Realthy male subjects (n = 5)  Ton et al. (2021)  Realthy male subjects (n = 5)  Ton et al. (2021)  Realthy male subjects (n = 5)  Ton et al. (2021)  Realthy male subjects (n = 8)  Realthy male subjects (n = 8)  Ton et al. (2021)  Realthy male subjects (n = 8)  Ton et al. (2021)  Realthy male subjects (n = 8)  Ton et al. (2021)  Realthy male subjects (n = 8)  Ton et al. (2021)  Realthy male subjects (n = 8)  Ton et al. (2021)  Realthy male subjects (n = 8)  Tone tal. (2021)  Realthy male subjects (n = 8)  Tone tal. (2021)  Tone-challenge Group 1: One-challenge Group 2: Control  Tone-challenge Group 2: One-challenge Group 2: Control  Tone tal. (2021)  Tone-challenge Tone expression (1.26 protein expression (1.24, 1.24)  Realthy male subjects (n = 8)  Tone tal. (2021)  Realthy male subjects (n = 8)  Tone tal. (2021)  Realthy male subjects (n = 8)  Tone tal. (2021)  Realthy male subjects (n = 8)  Tone tal. (2021)  Realthy male subjects (n = 8)  Tone a protein expression: 2.08 (2.02)  Tone challenge Group 2: Control  Tone-challenge Tryle-a protein expression: 2.08 (2.02)  Tone-challenge Tryle-a protein expression: 0.09 (0.58, 0.98)  Tone-a protein expression: 0.09 (0.98, 0								2.53, -0.49)
Control   Subjects   Control   Subjects   Control   C	11	Peters van	Human	Intravenous LPS	1.5h	Group 1: One-challenge	TNF-α protein expression	(Positive favours one-challenge)
Country   Subjects (n = 5)   Sh   Sh   Group 1: One-challenge Group 2: Control   TNF-α protein expression   TNF-α protein expr		Ton et al.	healthy male	challenges (2		Group 2: Control		TNF-α protein expression: 2.33
ThF-α protein expression: 1.22 (-0.20, 2.64)   Country		(2021)	subjects					
2h   2h   2h   2h   2h   2h   2h   2h			(n = 5)		8h	Group 1: One-challenge	TNF-α protein expression	(Positive favours one-challenge)
Part						Group 2: Control		TNF-α protein expression: 1.22 (-
The protein expression: 2.86 (0.83, 4.89) (Positive favours one-challenge)   II6 protein expression: 0.00 (-1.24, 1.24) (Negative favours one-challenge)   II6 protein expression: 0.00 (-1.24, 1.24) (Negative favours one-challenge)   II6 protein expression: 0.00 (-1.24, 1.24) (Negative favours one-challenge)   II6 protein expression: 0.00 (-1.24, 1.24) (Negative favours one-challenge)   II6 protein expression: 0.00 (-1.24, 1.24) (Negative favours one-challenge)   II6 protein expression: 0.00 (-1.24, 1.24) (Negative favours one-challenge)   II6 protein expression: 0.00 (-1.24, 1.24) (Negative favours one-challenge)   II6 protein expression: 0.00 (-1.24, 1.24) (Negative favours one-challenge)   II6 protein expression: 0.00 (-1.24, 1.24) (Negative favours one-challenge)   II6 protein expression: 0.00 (-1.24, 1.24) (Negative favours one-challenge)   II6 protein expression: 0.00 (-1.24, 1.24) (Negative favours one-challenge)   II6 protein expression: 0.00 (-1.24, 1.24) (Negative favours one-challenge)   II6 protein expression: 0.00 (-1.24, 1.24) (Negative favours one-challenge)   II6 protein expression: 0.00 (-1.24)								
12   Van 't Veer et al. (2007)   Human healthy male subjects (n = 8)   Administration with LPS (4 ng/kg) (1*), exvivo whole blood stimulated with 100 ng/mL LPS (2**)   24h (2***)   24h (2***)   24h (2****)   24h (2*****)   24h (2*****)   24h (2*****)   24h (2*****)   24h (2******)   24h (2********)   24h (2*********)   24h (2************************************					2h		IL-6 protein expression	
Positive favours one-challenge   RaK3 mRNA expression   TNF-α protein ex						Group 2: Control		
Left protein expression   Left protein expression   Left protein expression   Left protein expression   O.O. (-1.24, 1.24)								
1.5h, 2h (1st)   1.5h, 2h (2st)   1.5								
12   van 't Veer et al. (2007)   healthy male subjects (n = 8)     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )   1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )     1.5h. 2h (2 <sup>nd</sup> )   2 <sup>nd</sup>					8h		IL-6 protein expression	
1.5h, 2h (1sh), 1.5h, 2h (2md)   2.5h, 2h (2md)   2.5h						Group 2: Control		
1.5h, 2h (2 <sup>nd</sup> )   1.5h, 2h (					1 51 01 (1st)	G 1 T		
12   van 't Veer et al. (2007)   Human healthy male subjects (n = 8)   Human healthy male subjects (n = 8)   I.5h   Group 1: One-challenge Group 2: Control   IRAK3 mRNA expression   (Negative favours one-challenge)   IRAK3 mRNA expression   (Positive favours one-challenge)   IRAK3 mRNA expression   (Regative favours one-challenge)   IRAK3 mRNA expression   IRAK3 mR							INF-α protein expression	
12   van 't Veer   et al. (2007)   healthy male subjects (n = 8)					1.5n, 2n (2 <sup>nd</sup> )		II 6 matein aymassism	
Van 't Veer   et al. (2007)   Human healthy male subjects (n = 8)   Administration with LPS (4 ng/kg)   Intravenous administration with LPS (4 ng/kg) (1st), exvivo whole blood stimulated with 100 ng/mL LPS (2nd)   LPS (						Group 2: One-channinge	1L-6 protein expression	
12 et al. (2007)Veer et al. (2007)Human healthy male subjects (n = 8)Administration with LPS (4 ng/kg)4h 1.5hGroup 1: One-challenge Group 2: ControlIRAK3 mRNA expression TNF-α protein expression(Positive favours one-challenge) IRAK3 mRNA expression: 1.76 (0.56, 2.97)TNF-α protein expressionTNF-α protein expressionTNF-α protein expression: 1.75 (0.55, 2.95)TNF-α protein expressionTNF-α protein expression: 1.75 (0.55, 2.95)TNF-α protein expression: 1.75 (0.55, 2.95)TNF-α protein expression: 0.00 (- 0.98, 0.98)TNF-α protein expression: 1.75 (0.55, 2.95)TNF-α protein expression: 0.00 (- 0.98, 0.98)TNF-α protein expression: 1.75 (0.55, 2.95)TNF-α protein expression: 0.00 (- 0.98, 0.98)TNF-α protein expression: 1.75 (0.55, 2.95)TNF-α protein expression: 0.00 (- 0.98, 0.98)TNF-α protein expression: 1.75 (0.55, 2.95)TNF-α protein expression: 0.00 (- 0.98, 0.98)TNF-α protein expression: 1.75 (0.55, 2.95)TNF-α protein expression: 0.00 (- 0.98, 0.98)TNF-α protein expression: 1.75 (0.55, 2.95)TNF-α protein expression: 0.00 (- 0.98, 0.98)TNF-α protein expression: 1.75 (0.55, 2.95)TNF-α protein expressio								
et al. (2007)   healthy male subjects (n = 8)   with LPS (4 ng/kg)   1.5h   Group 1: One-challenge Group 2: Control   TNF-α protein expression   O.98, 0.98)   (Negative favours one-challenge)   TNF-α protein expression   TNF-α protein expression   TNF-α protein expression   TNF-α protein expression   O.98, 0.98)   (Negative favours one-challenge)   TNF-α protein expression   TNF-α protein expression   TNF-α protein expression   TNF-α protein expression   O.98, 0.98)   (Negative favours one-challenge)   TNF-α protein expression   TNF-α protein expression   TNF-α protein expression   TNF-α protein expression   O.98, 0.98)   (Negative favours one-challenge)   TNF-α protein expression   TNF-α protein expression   TNF-α protein expression   TNF-α protein expression   O.98, 0.98)   (Negative favours one-challenge)   TNF-α protein expression   TNF-α protein expression   O.98, 0.98)   (Negative favours one-challenge)   TNF-α protein expression	12	van 't Veer	Human	Administration	∕lh	Group 1: One-challenge	IRAK3 mRNA expression	
$ \begin{array}{c} \text{subjects} \\ (n=8) \end{array} \begin{array}{c} \text{ng/kg}) \\ \text{n=8} \end{array} \begin{array}{c} \text{ng/kg}) \\ \text{n=8} \end{array} \begin{array}{c} \text{1.5h} \\ \text{n=8} \end{array} \begin{array}{c} \text{Group 1: One-challenge} \\ \text{Group 2: Control} \end{array} \end{array} \begin{array}{c} \text{TNF-$\alpha$ protein expression} \\ \text{TNF-$\alpha$ protein expression} \end{array} \begin{array}{c} (0.56, 2.97) \\ \text{(Positive favours one-challenge} \\ \text{TNF-$\alpha$ protein expression} \end{array} \end{array} \begin{array}{c} \text{TNF-$\alpha$ protein expression} \\ \text{(0.56, 2.97)} \end{array} \begin{array}{c} (0.56, 2.97) \\ \text{(Positive favours one-challenge} \\ \text{TNF-$\alpha$ protein expression} \end{array} \begin{array}{c} TNF-$\alpha$ protein ex$	12				711		individe apression	
(n = 8)  (n = 7NF-α protein expression: 0.00 (-0.98, 0.98)  (n = 3)  (n = 8)  (n =		(2007)	•			eroup 2. common		
Group 2: Control  4h  Group 1: One-challenge Group 2: Control  TNF-α protein expression: 1.75 (0.55, 2.95)  TNF-α protein expression: 0.00 (-0.98, 0.98)  TNF-α				8/8/	1.5h	Group 1: One-challenge	TNF-α protein expression	
A			, ,					
Group 2: Control Group 1: One-challenge Group 2: Control Group 1: Two- challenges Group 2: One-challenge TNF-α protein expression (Negative favours one-challenge) TNF-α protein expression: 0.00 (- 0.98, 0.98) (Negative favours one-challenge) TNF-α protein expression: -0.60 (- 1.61, 0.41)						•		(0.55, 2.95)
Intravenous administration with LPS (4 ng/kg) (1st), ex vivo whole blood stimulated with 100 ng/mL LPS (2nd)  Intravenous administration with 100 ng/mL LPS (2nd)  Intravenous administration with LPS (2nd)  Intravenous administration with LPS (4 ng/kg) (1st), ex vivo whole blood stimulated with 100 ng/mL LPS (2nd)  Intravenous administration (1st), 24h (2nd)  Intravenous adminis					4h		TNF-α protein expression	TNF-α protein expression: 0.00 (-
Intravenous administration with LPS (4 ng/kg) (1st), ex vivo whole blood stimulated with 100 ng/mL LPS (2 <sup>nd</sup> )  LPS (2 <sup>nd</sup> )  Group 2: Control Group 1: Two-challenges  Group 2: Control Group 1: Two-challenges  Group 2: Control Group 1: Two-challenges  TNF-α protein expression  (Negative favours one-challenge)  TNF-α protein expression: -0.60 (-1.61, 0.41)								
Intravenous administration with LPS (4 ng/kg) (1 <sup>st</sup> ), ex vivo whole blood stimulated with 100 ng/mL LPS (2 <sup>nd</sup> )  LPS (2 <sup>nd</sup> )  Intravenous administration with LPS (4 ng/kg) (1 <sup>st</sup> ), ex vivo whole blood stimulated with 100 ng/mL LPS (2 <sup>nd</sup> )  Intravenous administration (Negative favours one-challenge) TNF-α protein expression (Negative favours one-challenge) TNF-α protein expression: -0.60 (-1.61, 0.41)					24h		TNF-α protein expression	
administration with LPS (4 ng/kg) (1st), ex vivo whole blood stimulated with 100 ng/mL LPS (2nd) $ \begin{array}{c ccccccccccccccccccccccccccccccccccc$								
with LPS (4 ng/kg) (1 <sup>st</sup> ), ex vivo whole blood stimulated with 100 ng/mL LPS (2 <sup>nd</sup> )  Group 2: One-challenge  1.61, 0.41)					\ //		TNF-α protein expression	
ng/kg) (1 <sup>st</sup> ), ex vivo whole blood stimulated with 100 ng/mL LPS (2 <sup>nd</sup> )					24h (2 <sup>nd</sup> )			
vivo whole blood stimulated with 100 ng/mL LPS (2 <sup>nd</sup> )						Group 2: One-challenge		1.61, 0.41)
blood stimulated with 100 ng/mL LPS (2 <sup>nd</sup> )								
with 100 ng/mL LPS (2 <sup>nd</sup> )								
LPS (2 <sup>nd</sup> )								
	Anim	al <i>in vivo</i> studi	06	LFS (2°)			1	

1	Aboyoussef et al. (2021)	Adult male albino rats (n = 10)	Cecal ligation and puncture (CLP)	24h	Group 1: One-challenge Group 2: Control	TNF-α protein expression  IL-6 protein expression	(Positive favours one-challenge) TNF-α protein expression: 9.43 (6.05, 12.81) (Positive favours one-challenge) IL-6 protein expression: 10.98 (7.08, 14.88)
2	Berglund et al. (2010)	C57BL/6 mice (n = 5-10)	3% DSS dissolved in tap water for a period of 5d followed by 2d of regular drinking water	7d	Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	TNF-α and IL-6 mRNA and protein expression	Not estimable
3	Deng et al. (2006)	C57BL/6J mice (n = 5)	Cecal ligation and puncture (CLP)	24h	Group 1: One-challenge Group 2: Control	IRAK3 mRNA expression	(Positive favours one-challenge) IRAK3 mRNA expression: 15.59 (4.78, 26.40)
			Inoculation with P. aeruginosa	24h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 2.19 (0.44, 3.93)
				6h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 1.70 (0.14, 3.27)
			CLP (1 <sup>st</sup> ); lung macrophages extracted and <i>ex vivo</i> challenged with LPS (1 µg/ml) (2 <sup>nd</sup> )	24h (1 <sup>st</sup> ), 6h (2 <sup>nd</sup> )	Group 1: Two- challenges Group 2: One-challenge	IRAK3 mRNA expression	(Positive favours two-challenge) IRAK3 mRNA expression: 1.14 (-0.45, 2.73)
			CLP (1st), macrophages extracted and ex vivo challenged with LPS (100 ng/ml) (2nd)	24h (1 <sup>st</sup> ), 16h (2 <sup>nd</sup> )	Group 1: Two- challenges Group 2: One-challenge	TNF-α protein expression	(Negative favours one-challenge) TNF-α protein expression: -1.05 (-2.42, 0.32)
			CLP (1st), inoculation with	24h (1 <sup>st</sup> ), 6h (2 <sup>nd</sup> )	Group 1: IRAK3 knockout	TNF-α mRNA expression	(Positive favours IRAK3 knockout)

			P. aeruginosa (2 <sup>nd</sup> )  CLP (1 <sup>st</sup> ), inoculation with P. aeruginosa (2 <sup>nd</sup> )	24h (1 <sup>st</sup> ), 24h (2 <sup>nd</sup> )	Group 2: IRAK3 wildtype Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	TNF-α protein expression	TNF-α mRNA expression: 1.39 (-0.29, 3.07)  (Positive favours IRAK3 knockout) TNF-α protein expression: 1.49 (0.00, 2.99)
4	Funahashi et al. (2019)	C57BL/6 mice (n = 6-7)	CLP	6h 24h 6h 24h	Group 1: One-challenge Group 2: Control  Group 1: One-challenge Group 2: Control	TNF-α protein expression  IL-6 protein expression	(Positive favours one-challenge) TNF-α protein expression: 0.72 (-0.47, 1.90) (Positive favours one-challenge) TNF-α protein expression: 0.56 (-0.56, 1.68) (Positive favours one-challenge) IL-6 protein expression: 2.34 (0.73, 3.95) (Positive favours one-challenge) IL-6 protein expression: 32.07 (18.02, 46.12)
5	Gandhirajan et al. (2021)	C57BL/6 mice (n = 5)	Intraperitoneally injected 250 µl cecal slurry (CS)-induced sepsis	4h, 24h	Group 1: One-challenge Group 2: Control	TNF-α and IL-6 protein expression	Not estimable
6	Gong et al. (2017)	C57BL/6 mice (n = 8)	Inhalation with LPS (100 μg/mL) for 30min	24h (outcomes measured after challenge)	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	TNF-α protein expression  IL-6 protein expression  TNF-α protein expression  IL-6 protein expression	(Positive favours one-challenge) TNF-α protein expression: 1.75 (0.55, 2.95) (Positive favours one-challenge) IL-6 protein expression: 6.37 (3.40, 9.35) (Positive favours IRAK3 knockout) TNF-α protein expression: 0.24 (-0.74, 1.23) (Negative favours IRAK3 wildtype)

			Cigarette smoking exposure (1st), inhalation with LPS (100 µg/mL) for 30min (2nd)	3d (1 <sup>st</sup> ), 24h (2 <sup>nd</sup> )	Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	TNF-α protein expression IL-6 protein expression	IL-6 protein expression: -0.93 (-2.05, 0.19) Not estimable.
7	Gribar <i>et al</i> . (2009)	C57BL/6 mice (n = 4)	Injected with LPS (5 mg/kg)	3h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 4.54 (1.12, 7.96)
8	Han et al. (2008)	BALB/c mice (n = 2)	Injection with 45 mg/kg LPS  Injection with 15 mg/kg LPS or 300 mg/kg pLTA (1st), injection with 45 mg/kg LPS (2nd)	24h (1 <sup>st</sup> ), 24h (2 <sup>nd</sup> )	Group 1: One-challenge Group 2: Control Group 1: Two- challenges Group 2: One-challenge	TNF-α protein expression TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 4.78 (- 22.33, 31.89) (Negative favours one-challenge) TNF-α protein expression: -3.43 (- 22.96, 16.09)
9	Hayashi et al. (2009)	C57BL/6 mice (n = 8-10)	Injection with LPS (2 μg per mouse) Injection with LPS (2 μg per mouse) Injection with 1V136, Pam3CSK4 or pIC Injection with 1V136 (1st), mice injected with 1V136, Pam3CSK4, pIC, LPS or ISS-ODN (2nd)	2h 2h 2-3h 3d (1st), 2h (2nd)	Group 1: One-challenge Group 2: Control  Group 1: One-challenge Group 2: Control  Group 1: One-challenge Group 2: Control  Group 1: Two-challenges Group 2: One-challenge	TNF-α protein expression  IL-6 protein expression  TNF-α and IL-6 protein expression  TNF-α and IL-6 protein expression	(Positive favours one-challenge) TNF-α protein expression: 1.60 (0.51, 2.70) (Positive favours one-challenge) IL-6 protein expression: 3.98 (2.24, 5.72) Not estimable

10	Hoogerwerf et al. (2012)	C57BL/6 (n = 8)	Infection with 1 $\times$ 10 <sup>4</sup> CFU of <i>K</i> .	24h	Group 1: One-challenge Group 2: Control	IRAK3 mRNA expression	(Positive favours one-challenge) IRAK3 mRNA expression: 2.84
			pneumoniae	3h 3h	Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	TNF-α protein expression	(1.34, 4.34) (Positive favours IRAK3 knockout) TNF-α protein expression: 0.46 (-0.54, 1.45)
				24h	Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	IL-6 protein expression	(Positive favours IRAK3 knockout) IL-6 protein expression: 0.57 (-0.43, 1.58)
				24h	Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	TNF-α protein expression	(Negative favours IRAK3 wildtype) TNF-α protein expression: -0.65 (-0.54, 1.45)
					Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	IL-6 protein expression	(Negative favours IRAK3 wildtype) IL-6 protein expression: -1.68 (-2.86, -0.49)
11	Kallapur et al. (2007)	Sheep $(n = 5 - 9/group)$	Injection with LPS (10 mg) twice (1st), lung or blood monocytes extracted and in vitro stimulated with LPS (100 ng/mL) (2nd)	2d and 7d (1 <sup>st</sup> ) 16h (2 <sup>nd</sup> )	Group 1: Two-challenges Group 2: One-challenge	IRAK3 protein expression	Not estimable
12	Kim et al. (2008)	BALB/c mice (n = 3)	$ \begin{array}{cccc} Injection & with \\ 10 & - & 40 \\ \mu g/mouse & \\ CpGDNA & \\ Injection & with \\ 10 & - & 40 \\ \mu g/mouse & \\ \end{array} $	24h (1 <sup>st</sup> ), 6h (2 <sup>nd</sup> )	Group 1: One-challenge Group 2: Control  Group 1: Two-challenges Group 2: One-challenge	IRAK3 protein expression	Not estimable  Not estimable

			CpGDNA (1st), CpGDNA (2nd)				
13	Kingsley et al. (2020)	Rats (n = 6)	Inoculation with 600 CFU of <i>E. coli</i> .	12h	Group 1: One-challenge Group 2: Control	TNF-α and IL-6 protein expression	(Positive favours one-challenge) TNF-α protein expression: 3.95 (1.71, 6.78) (Positive favours one-challenge) IL-6 protein expression: 12.22 (6.15, 18.29)
14	Krogmann et al. (2020)	C57BL/6J mice (n = 2-4)	Injected mice with 20-100 μg R848 (TLR7 ligand)	2h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	Not estimable
15	Li et al. (2013)	BALB/c mice (n = 3-6)	Injection with LPS (0.2 mg/kg) (1st), injection with LPS (10 mg/kg) (2nd)	24h (1 <sup>st</sup> ), 3h (2 <sup>nd</sup> )	Group 1: Two- challenges Group 2: One-challenge	IRAK3 protein expression (n = 3)  TNF-α protein expression (n = 6)	(Positive favours two-challenge) IRAK3 protein expression: 5.71 (-0.03, 11.45) (Negative favours one-challenge) TNF-α protein expression: -11.99 (-17.95, -6.03)
16	Li et al. (2016)	Pig (n = 3)	Oral administration with <i>E. coli</i> (1 × 10 <sup>9</sup> CFU/kg).	3h	Group 1: One-challenge Group 2: Control	IRAK3 mRNA expression TNF-α protein expression	Not estimable
			Diet supplemented with <i>L. acidophilus</i> (1 <sup>st</sup> ), oral administration with <i>E. coli</i> (1 × 10 <sup>9</sup> CFU/kg)	14d (1 <sup>st</sup> ), 3h (2 <sup>nd</sup> )	Group 1: Two- challenges Group 2: One-challenge	IRAK3 mRNA expression TNF-α protein expression	Not estimable
17	Lyn-Kew et al. (2010)	C57BL/6J mice (n = 5)	CLP	24h 24h	Group 1: One-challenge Group 2: Control Group 1: IRAK3 knockout	IRAK3 mRNA expression  TNF-α mRNA expression	(Positive favours one-challenge) IRAK3 mRNA expression: 4.29 (- 0.15, 8.72) (Positive favours IRAK3 knockout)

			CLP (1 <sup>st</sup> ); pulmonary macrophages extracted and stimulated 1 mg/ml LPS (n = 3)	24h (1 <sup>st</sup> ), 4h (2 <sup>nd</sup> )	Group 2: IRAK3 wildtype Group 1: Two- challenges Group 2: One-challenge Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	IRAK3 mRNA expression  TNF-α mRNA expression	TNF-α mRNA expression: 1.16 (-0.24, 2.57) (Positive favours two-challenges) IRAK3 mRNA expression: 4.06 (-0.17, 8.29)  (Positive favours IRAK3 knockout) TNF-α mRNA expression: 1.81 (0.20, 3.41)
18	Miyata <i>et al</i> . (2015)	C57BL/6J mice	Inoculation with 1x10 <sup>7</sup> to 5x10 <sup>8</sup> CFU of Haemophilus influenzae	24h	Group 1: One-challenge Group 2: Control  Group 1: IRAK3 knockout Group 2: IRAK3 wildtype  Group 1: IRAK3 knockout Group 2: IRAK3 wildtype  Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	IRAK3 mRNA expression  TNF-α mRNA expression  TNF-α protein expression  IL-6 protein expression	(Positive favours one-challenge) IRAK3 mRNA expression: 9.61 (0.19, 19.03)  (Positive favours IRAK3 knockout) TNF-α mRNA expression: 1.84 (-0.55, 4.23) (Positive favours IRAK3 knockout) TNF-α protein expression: 1.74 (0.62, 2.87) (Positive favours IRAK3 knockout) IL-6 protein expression: 1.73 (0.60, 2.85)
19	Paik et al. (2019)	C57BL/6 mice (n = 3)	Administration with LPS (30 mg/kg)	18h	Group 1: One-challenge Group 2: Control	TNF-α protein expression  IL-6 protein expression	(Positive favours one-challenge) TNF-α protein expression: 16.86 (0.50, 33.22) (Positive favours one-challenge) IL-6 protein expression: 6.35 (0.01, 12.69)
20	Petzl <i>et al</i> . (2012)	Cow	Inoculation with <i>E. coli</i> .	24h	Group 1: One-challenge Group 2: Control	IRAK3 mRNA expression	Not estimable

			Inoculation with LPS (1st), inoculation with <i>E. coli</i> (2 <sup>nd</sup> ).	72h or 240h (1 <sup>st</sup> ), 24h (2 <sup>nd</sup> )	Group 1: Two- challenges Group 2: One-challenge	IRAK3 mRNA expression	Not estimable
21	Rothschild et al. (2017)	Mice (n = 3-4)	3-5% DSS dissolved in tap water for a period of 5d followed by 2d of regular drinking water	7d	Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	IL-6 protein expression	Not estimable
22	Shao <i>et al.</i> (2011)	C57BL/6 mice (n = 3)	Injection with LPS (0.1-0.5 μg/g)	1h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 2.43 (-0.41, 5.27) TNF-α protein expression: 0.00 (-
				6h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	0.16, 0.16) (Negative favours control)
				24h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	TNF-α protein expression: -0.35 (-1.99, 1.28) (Positive favours one-challenge)
				1h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	TNF-α protein expression: 9.10 (0.17, 18.03) (Positive favours one-challenge)
				6h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	TNF-α protein expression: 1.14 (-0.80, 3.08) TNF-α protein expression: 0.00 (-
				24h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	1.60, 1.60)
23	Szatanik et al. (2011)	BALB/c mice (n = 6)	Injection with 5x10 <sup>6</sup> CFU of <i>N. meningitides</i>	2h, 6h, 24h	Group 1: One-challenge group Group 2: lack of control	TNF-α and IL-6 protein expression	Not estimable
24	Takebayashi et al. (2009)	IQI/Jic mice (n = 6)	Intraperitoneal administration with 0.3 - 0.4 mg LPS	2h - 3h	Group 1: One-challenge Group 2: Control	IRAK3 mRNA expression	Not estimable
25	Tan <i>et al.</i> (2019)	Wistar rats	Injection with LPS (0.4 mg/rat)	4h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge)

				16h			TNF-α protein expression: 8.22 (6.67, 9.77) (Positive favours one-challenge) TNF-α protein expression: 11.33 (9.24, 13.41)
26	Tseng <i>et al</i> . (2020)	Sprague- Dawley rats (n = 6)	Injection with LPS (10 mg/kg)	24h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 3.81 (1.64, 5.99)
						IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 5.75 (2.73, 8.78)
27	van der Windt <i>et al</i> . (2012)	C57BL/6 mice (n = 8)	Inoculation with 5×10 <sup>4</sup> CFUs of <i>S. pneumoniae</i>	3h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 1.17 (0.08, 2.25)
				24h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 1.42 (0.29, 2.55)
				3h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 3.60 (1.86, 5.35)
				24h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 1.22 (0.13, 2.32)
				3h	Group 1: IRAK3 knockout Group 2: IRAK3	TNF-α protein expression	(Positive favours IRAK3 knockout) TNF-α protein expression: 0.13 (-
				24h	wildtype  Group 1: IRAK3	TNF-α protein expression	0.85, 1.11) (Positive favours IRAK3 knockout)
				3h	knockout Group 2: IRAK3 wildtype	TNF-α protein expression	TNF-α protein expression: 0.88 (-0.90, 1.06)
				24h	Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	IL-6 protein expression	(Positive favours IRAK3 knockout) IL-6 protein expression: 0.13 (-0.85, 1.11)

					Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	IL-6 protein expression	(Negative favours IRAK3 wildtype) IL-6 protein expression: -0.09 (-1.07, 0.89)
28	Xia et al. (2018)	C57BL/6 mice (n = 6)	CLP (1st), injection with LPS (10 mg/kg)	3d (1 <sup>st</sup> ), 24h (2 <sup>nd</sup> )	Group 1: Two- challenges Group 2: One-challenge	IRAK3 mRNA expression	(Positive favours two-challenge) IRAK3 mRNA expression: 4.91 (2.26, 7.56)
			(2 <sup>nd</sup> )			TNF-α protein expression	(Negative favours one-challenge) TNF-α protein expression: -2.84 (-4.63, 1.05)
					Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	TNF-α protein expression	(Positive favours IRAK3 knockout) TNF-α protein expression: 2.33 (0.73, 3.94)
29	Xie <i>et al</i> . (2019)	C57BL/6 mice (n = 10)	Injection with LPS (40 µg/kg)	24h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 14.61 (9.48, 19.74)
						IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 8.02 (5.11, 10.92)
30	Xiong et al. (2011)	C57BL/6J mice (n = 3)	Inoculation with LPS (25 µg/ mouse)	24h	Group 1: One-challenge Group 2: Control	IRAK3 mRNA expression	(Positive favours one-challenge) IRAK3 mRNA expression: 6.36 (0.01, 12.71)
			Inoculation with LPS (25 µg/mouse), macrophages extracted and treated with 100 ng/ml LPS	24h (1 <sup>st</sup> ), 3 h (2 <sup>nd</sup> )	Group 1: Two- challenges Group 2: One-challenge	TNF-α mRNA expression	Not estimable
31	Yang and Zhao (2021)	Rats (n = 12)	Injection with LPS (3mg/kg)	48h	Group 1: One-challenge Group 2: Control	TNF-α and IL-6 protein expression	(Positive favours one-challenge) TNF-α protein expression: 3.78 (2.36, 5.20) (Positive favours one-challenge)

							IL-6 protein expression: 3.31 (2.01, 4.61)
32	Yee and Hameman (2013)	C57BL/6 mice	Injection with LPS (1 mg/kg)	2h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 16.50 (11.06, 21.95)
	(2013)			4h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 8.02 (5.27, 10.76)
				2h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 1.93 (0.88, 2.97)
				4h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 3.45 (2.05, 4.85)
33	Yu et al. (2017)	Wistar rats	Injection with LPS (200 μg per mouse)	24h	Group 1: One-challenge Group 2: Control	IRAK3 mRNA expression	(Positive favours one-challenge) IRAK3 mRNA expression: 4.78 (2.91, 6.66)
			Daily injection with LPS (0.1 mg/kg LPS) (1st), on day 6 injection with LPS (200 µg per mouse)	5d (1 <sup>st</sup> ), 24h (2 <sup>nd</sup> ).	Group 1: Two-challenges Group 2: One-challenge	IRAK3 protein expression	(Positive favours two-challenge) IRAK3 protein expression: 3.03 (1.67, 4.40)
34	Zhang <i>et al</i> . (2020)	C57BL/6 mice (n = 6)	CLP	24h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 4.28 (1.91, 6.66)
35	Zhang and Wang (2021)	Male Sprague- Dawley rats (n = 6)	5.5% (w/v) dextran sodium sulfate-treated rats	7d	Group 1: One-challenge Group 2: Control	TNF-α and IL-6 protein expression	Not estimable
36	Zhao et al. (2019)	BALB/c mice (n = 11)	Injection with LPS (10mg/kg)	2h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 2.36 (1.22, 3.50)
				6h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge)

				2h	Group 1: One-challenge	IL-6 protein expression	TNF-α protein expression: 2.45 (1.29, 3.60)
					Group 2: Control		(Positive favours one-challenge)
				6h	Group 1: One challenge	IL-6 protein expression	IL-6 protein expression: 3.24 (1.89, 4.59)
				OII	Group 1: One-challenge	1L-0 protein expression	
					Group 2: Control		(Positive favours one-challenge)
							IL-6 protein expression: 3.66
							(2.21, 5.12)
37	Zhao et al.	BALB/c	Injection with	24h	Group 1: One-challenge	TNF-α protein expression	(Positive favours one-challenge)
	(2021)	mice $(n = 10)$	LPS (2mg/kg)		Group 2: Control		TNF-α protein expression: 48.09
					_		(31.44, 64.75)
						IL-6 protein expression	(Positive favours one-challenge)
							IL-6 protein expression: 48.50
							(31.71, 65.30)