

		Half a syringe	
		Marrow exposed to dry air on:	Marrow dehydration for:
6 July	8 pm	21 June	15 d*
7 July	9 am	23 June	14 d*
7 July	6 pm	25 June	12 d*
8 July	9 am	27 June	11 d*
8 July	6 pm	29 June	9 d*
9 July	11 am	1 July	8 d*
10 July	11 am	3 July	7 d*
11 July	11 am	5 July	6 d**
12 July	11 am	7 July	5 d**
13 July	11 am	9 July	4 d**
14 July	11 am	11 July	3 d**
15 July	11 am	13 July	2 d**
16 July	11 am	15 July	1 d**

*Nonvirulent in rabbits.

**Virulent in rabbits.

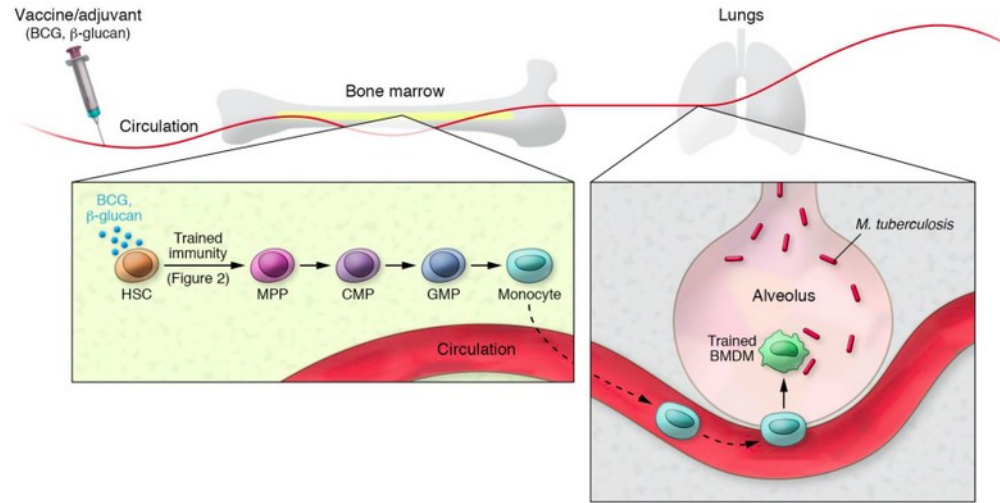
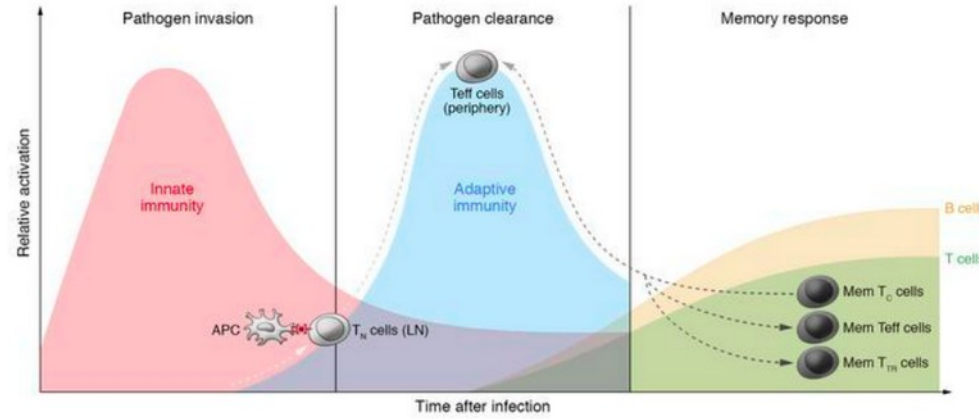


Licence: Public Domain Mark
Credit: The Pasteur Institute,
Kasauli, India: production of the
rabies vaccine: caged rabbits
showing symptoms of rabies
after inoculation. Photograph,
ca. 1910.



Licence: Public Domain
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Credit: The Pasteur
Institute, Kasauli, India:
production of the rabies
vaccine: a rabbit, under
anaesthetic, being
infected with rabies by
injection in the spine.
Photograph, ca. 1910.



Khader SA, Divangahi M, Hanekom W, Hill PC, Maeurer M, Makar KW, Mayer-Barber KD, Mhlanga MM, Nemes E, Schlesinger LS, van Crevel R, Vankayalapati R, Xavier RJ, Netea MG; Bill and Melinda Gates Foundation Collaboration for TB Vaccine Discovery Innate Immunity Working Group¹⁸. Targeting innate immunity for tuberculosis vaccination. *J Clin Invest*. 2019 Sep 3;129(9):3482-3491. doi: 10.1172/JCI128877. PMID: 31478909; PMCID: PMC6715374.

Sepulveda-Crespo D, Resino S, Martinez I. Innate Immune Response against Hepatitis C Virus: Targets for Vaccine Adjuvants. *Vaccines* (Basel). 2020 Jun 17;8(2):313. doi: 10.3390/vaccines8020313. PMID: 32560440; PMCID: PMC7350220.

PRR Type	Class of Activated Innate Receptor/Pathway	Adjuvant Name	Composition	Main Stimulated Immune Responses
TLRs	TLR3	Poly(I:C) or Poly(I:C) stabilized with poly-L-lysine	dsRNA analogs	Ab response, CD8 ⁺ T-cell response, Th1 type immunity
	TLR4	MPLA, GLA-SE, RC-529	MPL GLA AGP	Ab response CD8 ⁺ T-cell response Th1 type immunity
	TLR5	Flagellin fused to antigen	Bacterial flagellin	Ab response, Th1/Th2 response
	TLR7, 8 or both	Imiquimod/R837 (TLR7), Resiquimod/R848 (TLR7/8), 3M-052 (TLR7/8)	Imidazoquinoline analogs	Ab response, CD4 ⁺ /CD8 ⁺ T-cell response, Th1 type immunity
	TLR9	CpG-ODN	Synthetic ODN with optimized CpG motifs	Ab response, CD8 ⁺ T-cell response, Th1 type immunity
NLRs	RIG-I MDA-5	M8, Defective interfering RNA	dsRNA analogs	Ab response, CD4 ⁺ /CD8 ⁺ T-cell response
RLRs	Nod1 Nod2	iE-DAP, MDP	Bacterial peptidoglycan analogs	Ab response
CDs	STING	c-di-GAMP	Bacterial cyclic dinucleotides	Ab response, CD8 ⁺ T-cell response, Th1 type immunity

Ab: Antibody; AGP: Aminoalkyl glucosaminide 4-phosphate; c-di-GAMP: Cyclic guanosine monophosphate-adenosine monophosphate dinucleotide; CDs: Cytosolic DNA sensor ligands; CpG: Cytosine-phosphate-guanine; dsRNA: Double-stranded RNA; GLA: Glucopyranosyl lipid-adjuvant; iE-DAP: γ -D-glutamyl-meso-diaminopimelic acid; MDA-5: Melanoma differentiation-associated gene 5; MDP: Muramyl dipeptide; MPLA: Monophosphoryl lipid A adjuvant; NLRs: Nucleotide-binding oligomerization domain-like receptors; Nod1/2: Nucleotide oligomerization domain 1/domain 2; ODN: Oligodeoxynucleotide; Poly(I:C): Polyinosinic:polycytidylic acid; PRRs: Pattern recognition receptors; RIG-I: Retinoic acid-inducible gene-I; RLRs: RIG-I-like receptors; STING: Stimulator of interferon genes; Th1/Th2: T-helper cell type 1/type 2; TLRs: Toll-like receptors.

Lee BY, Mueller LE, Tilchin CG. A systems approach to vaccine decision making. *Vaccine*. 2017 Jan 20;35 Suppl 1(Suppl 1):A36-A42. doi: 10.1016/j.vaccine.2016.11.033. Epub 2016 Dec 22. PMID: 28017430; PMCID: PMC5460980.

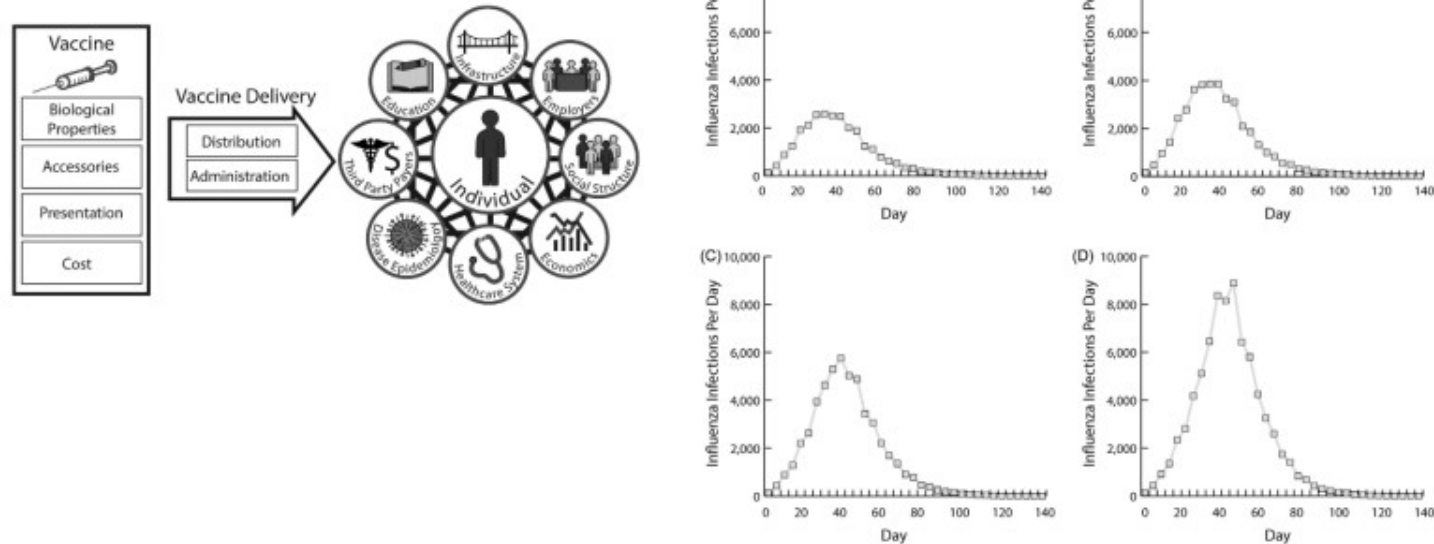
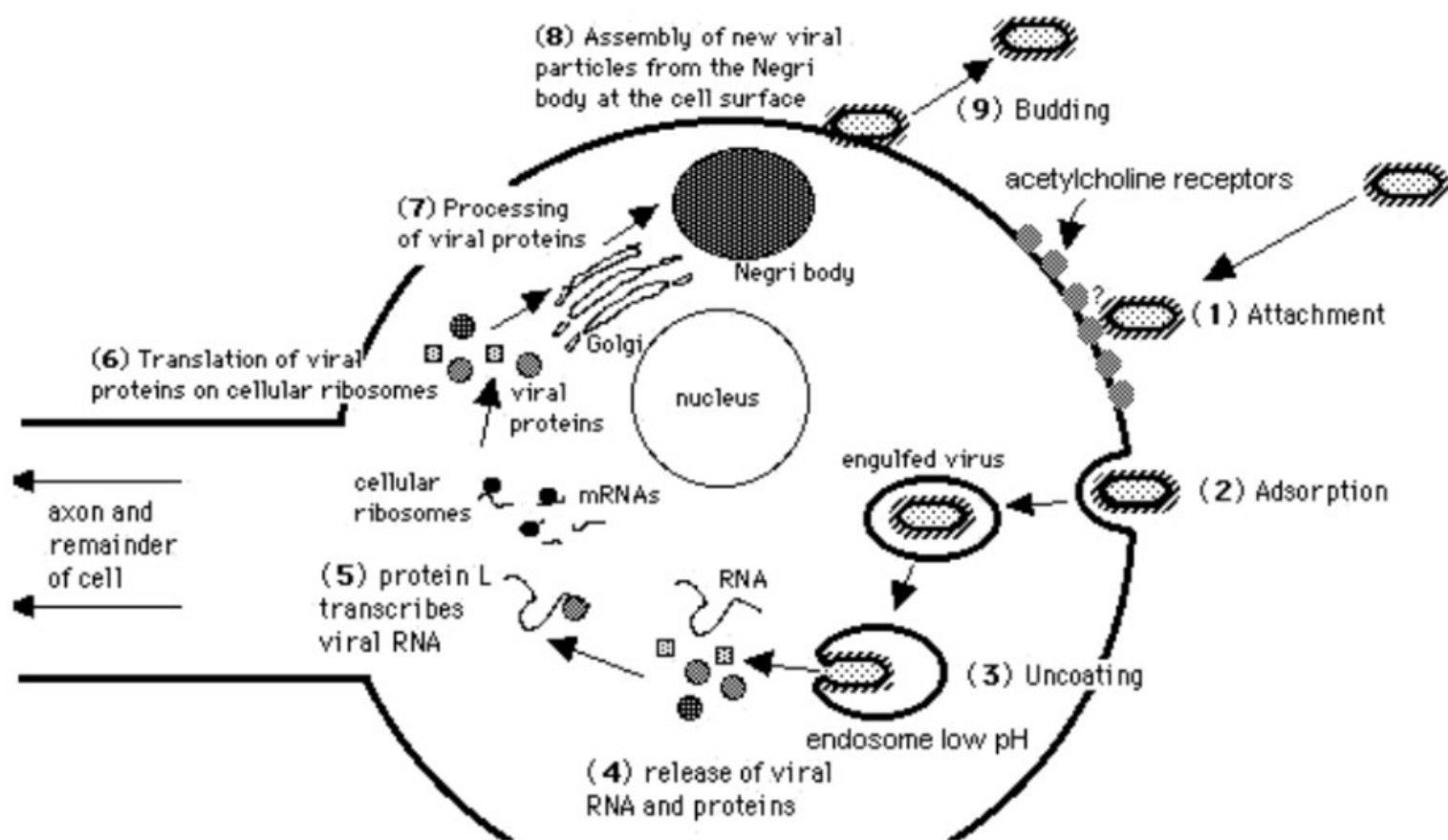


Fig. 5. Number of new influenza infections each day when two lowest-income counties experience vaccination delays of (a) 0 days, (b) 10 days, (c) 20 days, or (d) 30 days compared to other counties.

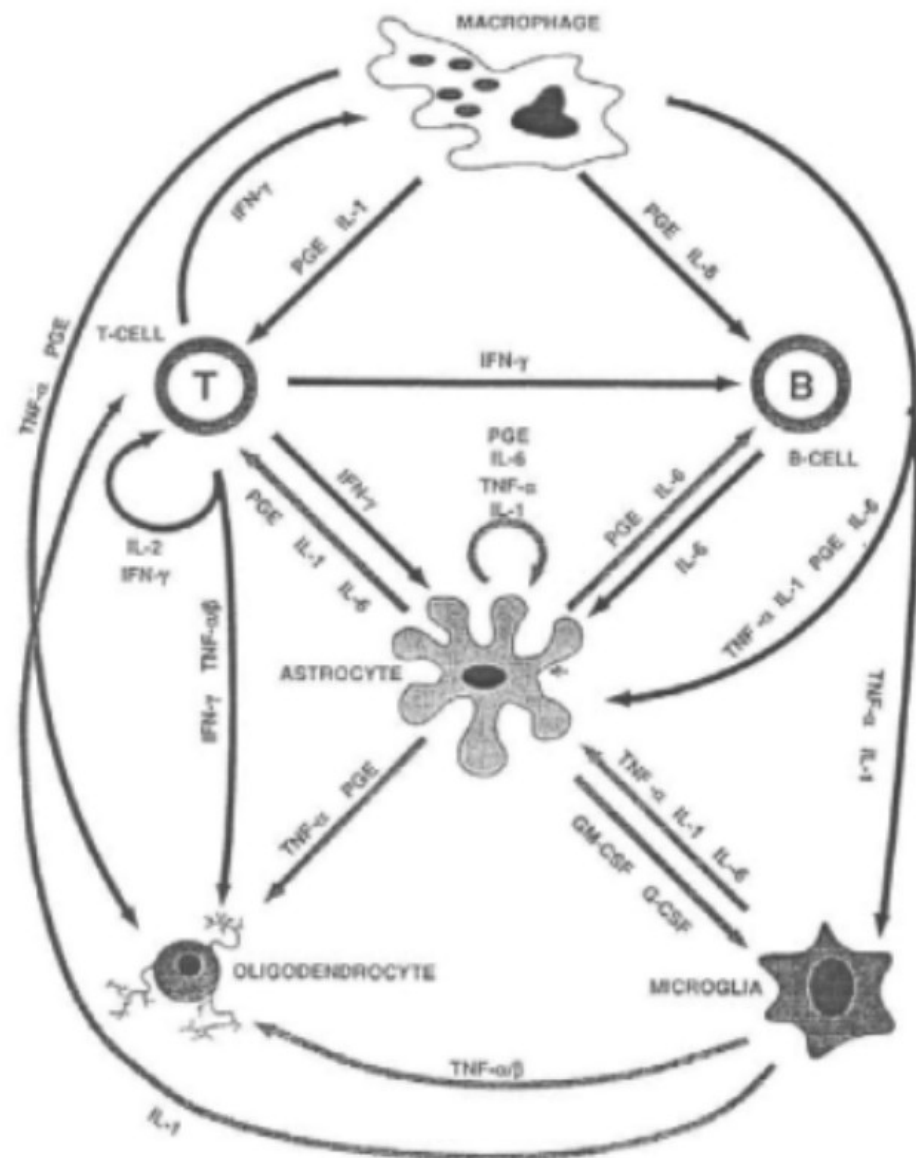
The mortality and severity of the target disease.
The safety of the vaccine candidate.
The full economic benefit of the vaccination program.

Host Cell (Neuron) Infection



J. Venom. Anim. Toxins incl. Trop. Dis.
 V.13, n.1, p.5-38 , 2007.
 Review article.
 ISSN 1678-9199.

Figure 2: Cycle of viral infection and replication. Adapted from Mazar



2

MAIN CLINICAL ABNORMALITIES

- Pneumothorax
- Intravascular thrombosis
- Secondary infections
- Pituitary dysfunction
- Hypoventilation, apnea
- Hypotension
- Cardiac arrhythmia, cardiac arrest
- Coma
- Hyperventilation, Hypoxia
- Aphasia. Incoordination.
- CNS signs; paresis. paralysis
- Hydrophobia, pharyngeal spasms
- Confusion, delirium. hallucinations
- Marked hyperactivity
- Anxiety, agitation, depression
- Fever
- Anorexia, nausea,
- Vomiting; headache
- Malaise, lethargy
- None
- Pain or Paresthesias at bite site

	Exposure	First symptom	First neurological sign	Onset of coma	Death occurs or recovery begins
Clinical Stage	Incubation	Prodrome	Acute neurological phase	Coma	Recovery
▼Period					
Usual Duration	20 to 90 days	2 to 10 days	2 to 7 days	0 to 14 days	Several months

SPECIMEN	TEST	DETECTION
ante mortem		
skin punch biopsy; repeat until a diagnosis is obtained	FAT test on frozen section RT-PCR	antigen detection viral RNA virus isolation
saliva, tears, CSF; repeat until a diagnosis is obtained	Tissue culture Suckling mouse inoculation RT-PCR	virus isolation viral RNA antibody detection
serum	Unvaccinated; test immediately*	antibody detection
CSF	Vaccinated; save and compare a few days later test immediately with serum*	antibody detection antibody detection
postmortem		
brain	FAT test of impressions smear	Antigen detection
needle necropsy** of two or more samples (brainstem and cerebellum)	RT-PCR suckling mouse inoculation	Viral RNA Viral isolation
retrospective diagnosis	enzyme methods	antigen detection in formalin-fixed tissue

FAT: Fluorescent antibody test

RT-PCR: Reverse transcription polymerase chain reaction

CSF: Cerebrospinal fluid

* In unvaccinated patients, rabies antibody generally appears in the second week of the disease. Rabies specific IgM has been detected in the serum and in some cases in the CSF at low concentration, but no earlier than IgG. High concentrations of antibody in the CSF have been considered diagnostic despite vaccination.

** Needle necropsy: with a Vim-Silverman's or other long biopsy needle.

Source: Warrell and Warrell, 2004 (94).

