Passive and active immunity

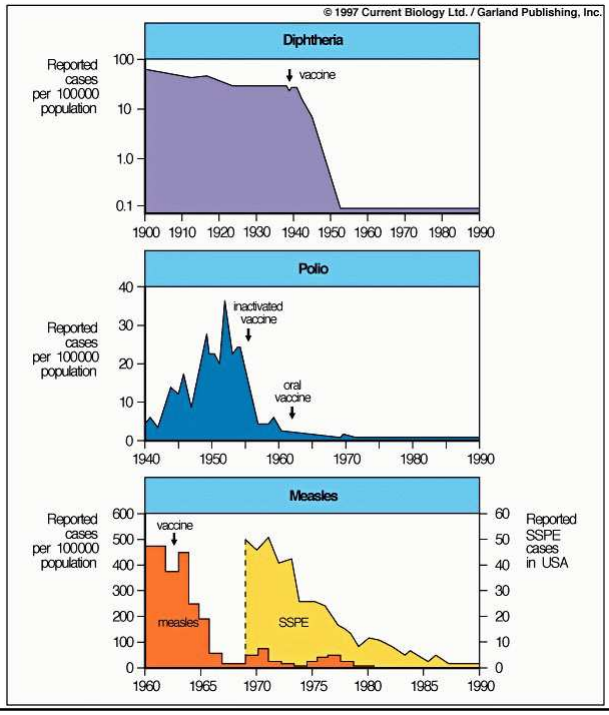
Passive

IV-IgG	
Human immune globulin	Postexposure prophylaxis (tetanus, rabies)
Monoclonal antibodies	Cancer cells, immune cells involved in graft rejection
Animal antitoxins	Animal and isects bites
Transplacental IgG	

Active

Natural Infection

Vaccination



Successful vaccination campaigns.
Diphtheria, polio, and measles and its consequences have been virtually eliminated in the USA, as shown in these three graphs. SSPE stands for subacute sclerosing panencephalitis, a brain disease that is a late consequence of measles infection in a few patients. When measles was prevented, SSPE disappeared 10–15 years later. However, as these diseases have not been eradicated worldwide, immunization must be maintained in a very high percentage of the population to prevent their reappearance.

Criteria for an effective vaccine

Features of effective vaccines	
Safe	Vaccine must not itself cause illness or death
Protective	Vaccine must protect against illness resulting from exposure to live pathogen
Gives sustained protection	Protection against illness must last for several years
Induces neutralizing antibody	Some pathogens (like poliovirus) infect cells that cannot be replaced (eg neurons). Neutralizing antibody is essential to prevent infection of such cells
Induces protective T cells	Some pathogens, particularly intracellular, are more effectively dealt with by cell-mediated responses
Practical considerations	Low cost-per-dose Biological stability Ease of administration Few side-effects

Immunesuppression (es.: HA and CD46 → DC and IL-12)

A vaccine antigen must provoke the proper type of immune response.
Knowing the proper type of effector mechanism of immunity greatly facilitates vaccine development

An effective vaccination program provides herd immunity —by lowering the number of susceptible members of a population, the natural reservoir of infected individuals in that population falls, reducing the probability of transmission of infection. Thus, even non-vaccinated members of a population may be protected from infection if the majority are vaccinated.

Microbial antigens targeted for vaccine development

Organisms	Antigenic target	Mechanisms of immunity
Bacteria	Toxins	Neutralization of toxin
	Capsular polysaccharides	Opsonophagocytic and Bacteriocidal killing
	Surface proteins	Opsonophagocytic killing and trabsmission blocking
Viruses	Capsid coat protein	Neutralization of infectivity
	Internal core antigens	CMI
Fungi	Capsular polysaccharides	Opsonophagocytic killing
	Surface proteins	Unknown
Protozoan parasites	Surface proteins	Antibody-mediated neutralization
		CMI

Effector mechanisms	Type of pathogen	Mediators of immunity
Opsonophagocytic killing	Bacteria	IgG IgM
	Fungi	Complement
	Some Viruses	Phagocytes
Microbicidal killing	Bacteria	IgG IgM
	Viruses	Complement
Mucosal immunity	Bacteria	IgA, IgG and IgM
	Viruses	Complement for IgG and IgM
	Fungi	Mucosal phagocytes
	Protozoan parasites	IgE
	Helminthic parasites	Eosinophil
DTH	Bacteria	CD4+ T cells
	Viruses	Activated macrophages
	Fungi	Cytokines
	Protozoan parasites	
	Helminthic parasites	
Cytotoxic cells	Some Bacteria	CD8+ T cells
	Viruses	NK cells
	Fungi	Eosinophils
	Protozoan parasites	Cytokines
	Helminthic parasites	Ab for ADCC

Table 1-1. Effectiveness of Vaccines for Some Common Infectious Diseases

Disease	Maximum number of cases (year)	Number of cases in 2004	Percent change
Diphtheria	206,939 (1921)	0	-99.99
Measles	894,134 (1941)	37	-99.99
Mumps	152,209 (1968)	236	-99.90
Pertussis	265,269 (1934)	18,957	-96.84
Polio (paralytic)	21,269 (1952)	0	-100.0
Rubella	57,686 (1969)	12	-99.98
Tetanus	1,560 (1923)	26	-98.33
Haemophilus influenzae type B	~20,000 (1984)	16	-99.92
Hepatitis B	26,611 (1985)	6,632	-75.08

This table illustrates the striking decrease in the incidence of selected infectious diseases for which effective vaccines have been developed.
Adapted from Orenstein WA, AR Hinman, KJ Bart, and SC Hadler. Immunization. In Mandell GL, JE Bennett, and R Dolin (eds). Principles and Practices of Infectious Diseases, 4th ed. Churchill Livingstone, New York, 1995, and Morbidity and Mortality Weekly Report 53:1213-1221, 2005.

VACCINI

- **Vaccination applies immunological principles to human health.** Adaptive immunity and the ability of lymphocytes to develop memory for a pathogen's antigens underlie vaccination. Active immunization is known as vaccination.
- **A wide range of antigen preparations are in use as vaccines,** from whole organisms to simple peptides and sugars. Living and non-living vaccines have important differences, living vaccines being generally more effective.
- **Adjuvants enhance antibody production,** and are usually required with non-living vaccines. They concentrate antigen at appropriate sites or induce cytokines.
- **Most vaccines are still given by injection,** but other routes are being investigated.
- **Vaccine efficacy needs to be reviewed from time to time**.
- **Vaccine safety is an overriding consideration.** The MMR controversy resulted in measles epidemics.
- **Vaccines in general use have variable success rates.** Some vaccines are reserved for special groups only and vaccines for parasitic and some other infections are only experimental.
- **Passive immunization can be life-saving.** The direct administration of antibodies still has a role to play in certain circumstances, for example when tetanus toxin is already in the circulation.
- **Non-specific immunotherapy can boost immune activity.** Non-specific immunization, for example by cytokines, may be of use in selected conditions.
- **Immunization against a variety of non-infectious conditions is being investigated.** Recombinant DNA technology will probably be the basis for the next generation of vaccines.

Strategies for Vaccine Development

- The birth of immunology as a science dates from Edward Jenner's successful vaccination against smallpox in 1796. The importance of prophylactic immunization against infectious diseases is best illustrated by the fact that worldwide programs of vaccination have led to the complete or nearly complete eradication of many of these diseases in developed countries.
- ***The success of active immunization in eradicating infectious disease is dependent on numerous factors:***
  - Vaccines are effective if the infectious agent does not establish latency, if it does not undergo much or any antigenic variation, and if it does not interfere with the host immune response. It is difficult to effectively vaccinate against microbes such as HIV, which establishes latent infection, is highly variable, and disables key components of the immune system.
  - Vaccines are most effective against infections that are limited to human hosts, and do not have animal reservoirs.
  - Vaccines induce protection against infections by stimulating the development of antibodies, long-lived effector cells, and memory cells. Most vaccines in routine use today work by inducing humoral immunity, and attempts to stimulate cell-mediated immune responses by vaccination are ongoing.

Table 15-6. Vaccine Approaches

Type of vaccine	Examples
Live attenuated or killed bacteria	BCG, cholera
Live attenuated viruses	Polio, rabies
Subunit (antigen) vaccines	Tetanus toxoid, diphtheria toxoid
Conjugate vaccines	*Haemophilus influenzae*, pneumococcus
Synthetic vaccines	Hepatitis (recombinant proteins)
Viral vectors	Clinical trials of HIV antigens in canarypox vector
DNA vaccines	Clinical trials ongoing for several infections

Abbreviations: BCG, bacillus Calmette-Guérin, HIV, human immunodeficiency virus.

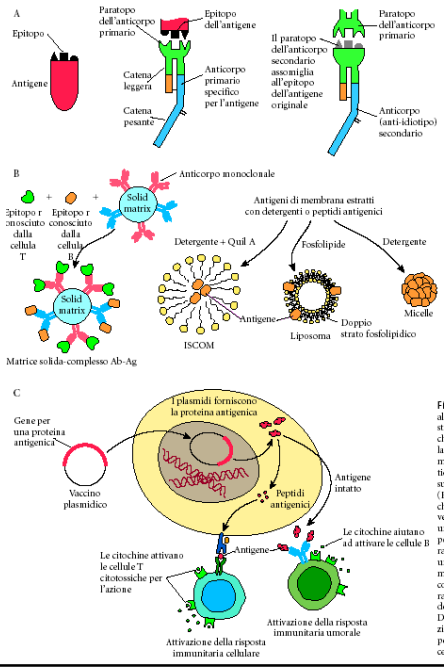


Figura 21.4 Principi di alcune delle più moderne strategie di vaccinazione che vengono valutati per la vaccinazione contro le malattie. (A) Uso degli anticorpi anti-idiotipo come surrogati degli antigeni. (B) Vaccini multivalenti che possono combinare diversi epitopi vaccinici in un unico vaccino. Tali vaccini possono, inoltre, incorporare antigeni vaccinici in una struttura liposomiale o micellare che può fondersi con le membrane per liberare gli antigeni all'interno delle cellule. (C) Vaccini a DNA permettono l'attivazione delle cellule T sia helper che citotossiche e delle cellule B.

ADIUVANTI

•Sostanze che co-introdotte con l'Ag aumentano l'antigenicità dell'Ag

•Sali di Alluminio o Allume (safe and TH2 → Ab)

•Maggior parte degli adiuvanti provocano infiammazione per rilascio di citochine chemochine infiammatorie e indirettamente

•Reclutamento di cellule infiammatorie nel sito di inoculo o attivazione dei linfociti T

•Attivano DC mediante TLR (lipoarabinomannano, peptidoglicano, LPS, zymosan) abbassando la concentrazione di Ag utile ad attivare la RI

•DNA CpG – TLR9 (incorporato in DNA ricombinante)

•Alfa-galattosil ceramide stimola una risposta CD8 ad antigeni "non-living" non sintetizzati per via endogena o attarverso il pathway citosolico

•Citochine (IL12, IFN-gamma, IL-4)

•Tossina colera e heat-labile toxin incrementano l'espressione dei marcatori di attivazione delle APC (MHC II, CD80 e CD86)

Adiuvanti

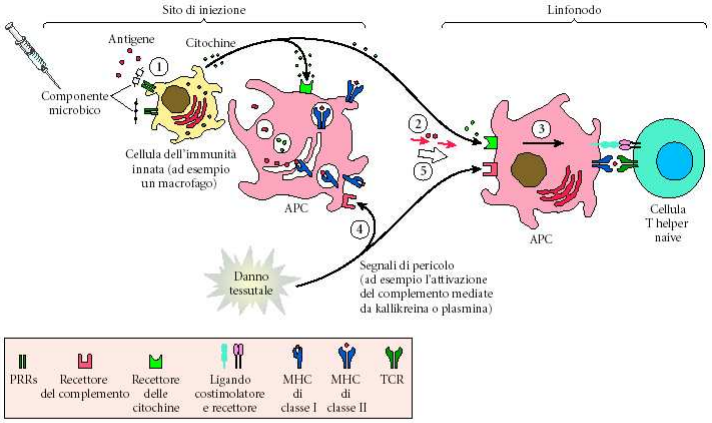


Figura 21.5 Visualizzazione delle tappe essenziali di differenti meccanismi adiuvanti. (1) Facilitazione del trasporto, dell'endocitosi e della presentazione dell'antigene mediati dalle cellule che catturano e che processano l'antigene nel linfonodo che sbocca nel sito d'inoculazione del vaccino. (2) Rilascio ripetuto o prolungato dell'antigene nei tessuti linfoidi (effetto locale). (3) La segnalazione mediata dai pattern-recognition-receptors (PRR) attiva le cellule dell'immunità innata a rilasciare le citochine necessarie per la maggiore espressione delle molecole costimolatorie. (4) Segnali di pericolo provenienti dai tessuti stressati o danneggiati stimolano le APC ad esprimere maggiormente le molecole costimolatorie. (5) Notare che la segnalazione da parte delle citochine ricombinanti o delle molecole costimolatorie mima la classica attività adiuvante. Tappe 3, 4 e 5 permettono il segnale 2 così come il segnale 1 da parte delle APC. Ristampato da V. E. Schijns, Curr. Opin. Immunol. 12:456-463, 2000, con autorizzazione.

Vie attraverso cui gli adiuvanti attivano le cellule

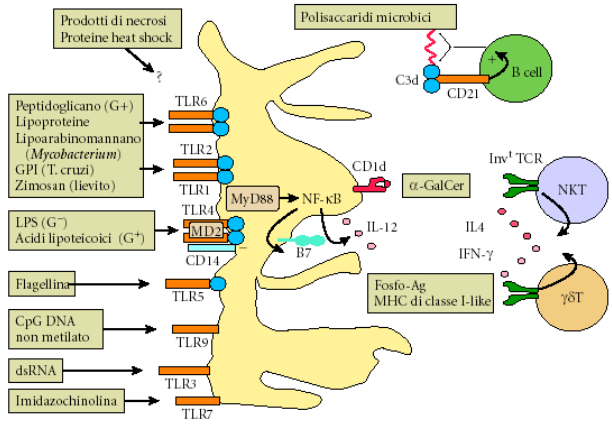


Figura 21.6 Vie attraverso cui gli adiuvanti attivano le cellule. I TLR trasducono i segnali in seguito al riconoscimento di specifiche strutture microbiche note per avere attività adiuvante. Composti che modificano la risposta immunitaria come l'imidazochinolina possono inoltre attivare le DC mediante il TLR7. I fattori solubili del complemento possono legare gli antigeni con il C3d e migliorare la risposta delle cellule B all'antigene. Le cellule T NK, che esprimono un recettore invariante delle cellule T (Inv⁺ TCR) e rispondono agli antigeni glicolipidici, come l'α-Gal-Cer, presentata dalle molecole MHC-like CD1, possono secernere citochine che aumentano le risposte delle cellule immunitarie verso gli antigeni copresenti. Riprodotto da A. Bendelac e R. Medzhitov, *J. Exp. Med.* 195:F19-F23, 2002, con autorizzazione.

HBV infection in Africa

- Hepatitis B virus infection is highly prevalent in Asia and Africa: the infection rate ranges 5-20% [Song EY, 2009]
- The prevalence of HBV is high in African countries: 14.3% HBV prevalence in Nigeria, 9.4% in Cote d'Ivoire and 12.4% in Burkina Faso [Ilboudo, 2002]
- In Nigeria pregnant women detected with HBsAg are 3.8%.
  In Burkina Faso 9.3% of pregnant women are infected by HBV (HBsAg-positive) [SimporeJ, 2004]
- Pregnant women infected with HBV are very likely to transmit the infection on to her infant
- In Burkina Faso the vertical transmission of HBV is 25%. [Ilboudo 2002]
- About 10-20% of infants born to hepatitis B infected mothers have been reported to be at risk of developing hepatitis.

Occult HBV infection

- Occult HBV infection is defined by serologically undetectable HBsAg despite the presence of HBV DNA in the sera or liver
- Occult HBV infection has its own risks of disease transmission and may contribute to acute exacerbation and development of HBV-associated diseases such as hepatic inflammation, cirrhosis, and hepatocellular carcinoma.
- **Increased risk of vertical transmission from mother to child**

HBV and immune system in children and newborn

- Vertical transmission has become the most important route of transmission of HBV in children after the introduction of the effective and safe vaccines in 1976/1982.
- Perinatal HBV transmission can be greatly reduced by proper immunoprophylaxis of exposed neonates.

BUT

- Unsatisfactory vaccine coverage and incomplete or delayed vaccine administration are still major problems
- In Hepatitis B infection, vaccine-induced neutralizing antibodies play an important role in protecting young infants from infection and the control of viral replication also involves T lymphocytes.

Infectious diseases and immune system in newborn

This increased susceptibility to infections is related to an immaturity of the immune system that also prevents the induction of protective immune responses by vaccines. *(Newborns have defective IFNγ response to vaccine such as polio)*

Immune responses at birth are often biased toward the Th2 type and defective in the Th1 type, the central defense mechanism against intracellular pathogens.

Human cord blood-derived dendritic cells have a profound defect in the production of IL-12, a cytokine playing a central role in the differentiation of Th1 lymphocytes.

Infectious diseases and immune system in newborn

Analysis of the Cytokine Production by Cord and Adult Blood

S. B. A. Cohen, I. Perez-Cruz, P. Fallen, E. Gluckman, and J. A. Madrigal(1999)

- T cells
  - CB lymphocytes are CD45RA, whereas the majority of adult lymphocytes are CD45RO. In the allogeneic setting and when cells are stimulated non-specifically, CB cells *per se also produce less cytokine.*
  - Frequency of T cells with the ability to produce TNFα, IFNγ, IL-2, IL-4 is reduced in CB compared to adult blood. This agrees with the observation that CB lymphocytes are naive, since they have not yet become primed to be Th1 or Th2 type cells.
- Antigen presenting capability
  - (through production of co-stimulatory cytokines) is reduced in CB compared to adult blood.

Infectious diseases and immune system in newborn

TABLE 1 Summary of comparisons between adult and cord blood cytokine production.

Cells	Stimulation	Analysis	Cytokine	Adult Blood	Cord Blood	Reference
CD45RA+ T cells	αCD2+αCD28±[1]PMA	[2]ELISA	IL-2	++	−	[11]
	Alloantigen	HTLp	IL-2	++	++	[a]Dr. A. M. Dickinson, Personal communication
	Alloantigen	ELISA	IFNγ	+++	++	[a]Dr. A. M. Dickinson, Personal communication
	[3]PHA	ELISA/[4]mRNA	TGF-β1	++	+	[28]
	PMA/PHA	mRNA	GM-CSF	+++	+	[29]
	Freezing/alloantigen	ELISA	IL-2	+++	++	[26]
	PMA plus Ionomycin	[5]Intracellular cytokine staining	IFNγ	+++	+	[30], Drs. [b]Bomstein & [g]Vela: Personal communication
			IL-2	+++	+	
			IL-4	+++	+	
			TNFα	+++	+	
NK cells	No stimulation	ELISA	IFNγ	+	−	[25], [31]
			IL-6	+	−	
			TNFα	+	−	
	IL-2 expansion	ELISA	IFNγ	ND	reduced	[24]
			IL-6	ND	constant	
			TNFα	ND	constant	
			IL-2R	ND	constant	
	IL-12	ELISA/mRNA	IFNγ	++	++	[25]
	PMA plus Ionomycin	ELISA/mRNA	IFNγ	+++	+	[25]
Antigen presenting cells	[6]LPS	ELISA/mRNA	IL-12	+++	+	[19]
	LPS	ELISA/mRNA	IL-15	+++	++	[20]
	Herpes Simplex Virus-1	[7]Bioassay	IFNα	+++	++	[f]Drs. L. Goldman & E. Katz, Personal communication
	PHA	ELISA/mRNA	TGF-β1	++	+	[28]
	PMA/PHA	mRNA	IL-8	++	+	[28]
	PMA/PHA	mRNA	GM-CSF	+++	+	[29]
	Freezing	ELISA	IL-10	+++	+++	[27]
Unknown	Alloantigen	ELISA	TNFα	++	+	[32]
	Alloantigen	ELISA	IL-10	++	++	[a]Dr. A. M. Dickinson, Personal communication [28]
	PMA/PHA	ELISA	MIP-1α	+++	+	

Infectious diseases and immune system in newborn

Defective antigen-presenting cell function in human neonates

Paula A. Velilla, Maria T. Rugelesa, Claire A. Chougnetb,*(2006)

Table 1 Findings supporting defective function of cord blood (CB) T cells and neonatal APCs

Findings that support defective function of CB T cells
- Low baseline expression of TCR/CD3 complex and adhesion molecules
- Blunted up-regulation of CD40L expression
- Defects in the production of cytokines
- Limited CD8 cytotoxic activity

Findings that support defective function of CB monocytes and macrophages
- Low basal levels of expression of costimulatory molecules by monocytes
- Unresponsiveness to LPS and IFN-γ of both monocytes and macrophages
- Reduced capacity of monocytes to differentiate into DCs
- Altered IL-12 production by PBMC
- Decreased phagocytic activity of CB macrophages

Findings that support defective function of CB dendritic cells
- Low basal expression of costimulatory molecules by CB-MDDC, CB mDCs and CB pDCs
- Altered maturation of CB-MDDC, CB mDCs and CB pDCs in response to TLR or CD40 signaling
- Defective production of cytokines by CB-MDDCs in response to TLR or CD40 signaling
- Decreased ability of CB-MDDCs and CB pDCs to stimulate allogeneic responses
- Reduced endocytic activity of CB-MDDCs

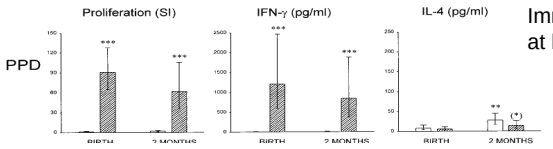
Bacillus Calmette-Guérin and Th1 response

Evaluation of BCG vaccine immunogenicity demonstrated that human newborns make strong Th1 responses to BCG detectable as long as one year suggesting immunological memory.

Newborns Develop a Th1-Type Immune Response to *Mycobacterium bovis* Bacillus Calmette-Guérin Vaccination[1]

Arnaud Marchant,[2]* Tessa Goetghebuer,* Martin O. Ota,* Ingrid Wolfe,* Serign J. Ceesay,* Donat De Groote,[†] Tumani Corrah,* Steve Bennett,[‡] Jeremy Wheeler,[‡] Kris Huygen,[§] Peter Aaby,[¶] Keith P. W. J. McAdam,* and Melanie J. Newport*

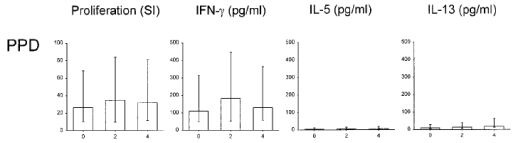
Data obtained in animals indicate that neonatal immune responses are biased toward Th2. This could reduce the efficacy of vaccines against viral and mycobacterial diseases. The ability of human newborns to develop a Th1 immune response upon immunization has not been studied. Since the vaccine *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) triggers a Th1-type response in adults, we investigated whether it induces a similar response in newborns and whether age at vaccination influences immunogenicity. We found that BCG vaccination at birth induces a memory Th1-type response of similar magnitude to that when given later in life. This study demonstrates that human newborns can be immunized against pathogens controlled by a Th1 immune response. *The Journal of Immunology*, 1999, 163: 2249–2255.



Immune response to BCG vaccination at birth

BCG

No BCG

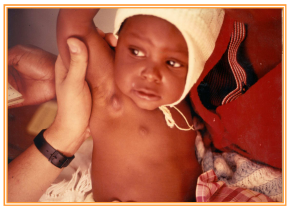


Memory immune response to BCG Vaccination at birth and at 2 mo and 4 mo of age

Bacillus Calmette-Guérin: advantages

BCG vaccine is recommended at birth and remains the only tuberculosis vaccine available for field usage.

BCG protects against forms of Tubercolosis in children with an efficacy of about 70%



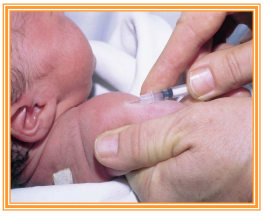
BCG protects against other protects against other mycobacteria (*M. leprae, M. ulcerans*)

BCG vaccination is associated with better survival in early childhood in areas with high mortality [Kristensen et al.; Br.Med.J.,2000]

The vaccination in humans is safe ($3x10^9$ administered doses)

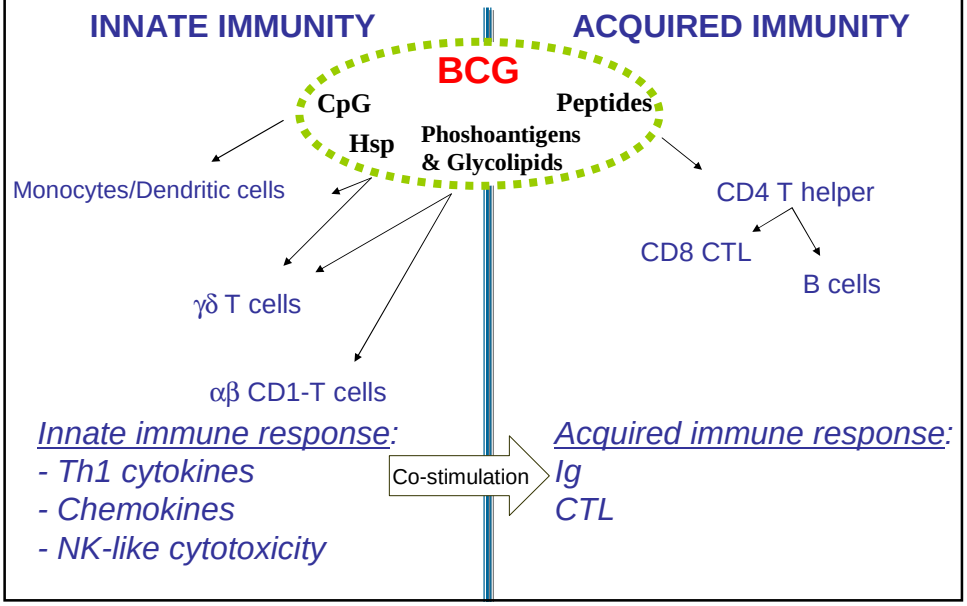
Bacillus Calmette-Guérin: advantages

BCG is routinely given to all the African baby during the first day of life.



BCG has been shown to possess a strong systemic and mucosal adjuvant activity, which can induce both humoral and cell-mediated immune response.

BCG may be capable of switching on multiple immune mechanisms



Bacillus Calmette-Guérin as adjuvant

BCG may be a useful Th1 inducing adjuvant at birth in humans.

It markedly increases the primary immune response to Hepatitis B vaccine in newborns and may have influence on infant memory responses.

Because immunization at birth generally primes the response of subsequent vaccine doses, new combinations of vaccines are an important public health endeavour.

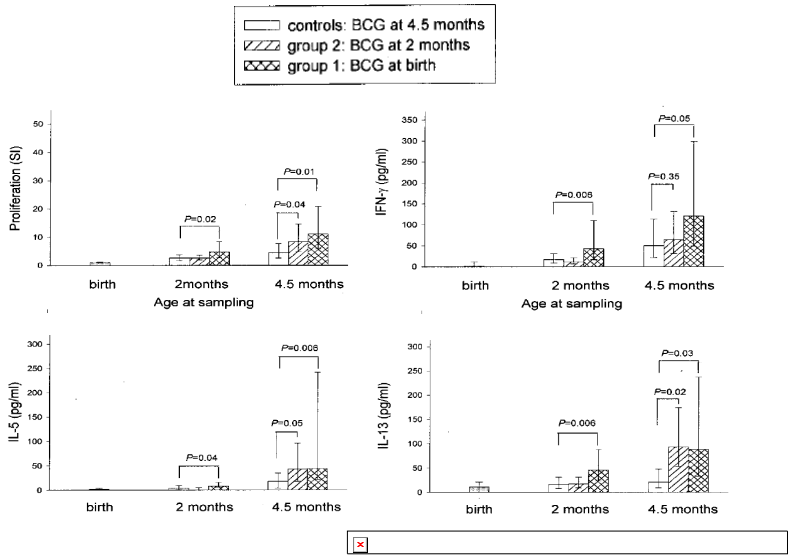
Influence of *Mycobacterium bovis* Bacillus Calmette-Guérin on Antibody and Cytokine Responses to Human Neonatal Vaccination[1]

Martin O. C. Ota,* Johan Vekemans,* Susanna E. Schlegel-Haueter,† Katherine Fielding,‡ Mariama Sanneh,* Michael Kidd,* Melanie J. Newport,§ Peter Aaby,¶ Hilton Whittle,* Paul-Henri Lambert,† Keith P. W. J. McAdam,* Claire-Anne Siegrist,† and Arnaud Marchant[2]*

The immaturity of the immune system increases the susceptibility of young infants to infectious diseases and prevents the induction of protective immune responses by vaccines. We previously reported that *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) vaccination induces a potent Th1 response to mycobacterial Ags in newborns. In this study, we evaluated the influence of BCG on the response to unrelated vaccines given in early life. Newborns were randomly allocated to one of three study groups receiving BCG at birth, when infants received their first dose of hepatitis B and oral polio vaccines; at 2 mo of age, when infants received their first dose of diphtheria and tetanus vaccines; or at 4.5 mo of age, when immune responses to vaccines were measured. Administration of BCG at the time of priming markedly increased the cellular and Ab responses to the hepatitis B vaccine, but had only a limited influence on the cytokine response to tetanus toxoid and no effect on the Ab responses to tetanus and diphtheria toxoids. Although BCG induced a potent Th1-type response to mycobacterial Ags, it promoted the production of both Th1- and Th2-type cytokines in response to unrelated vaccines. The effect of BCG was apparent at the systemic level, as it increased the Ab response to oral polio vaccine. These results demonstrate that BCG influences the immune response to unrelated Ags in early life, likely through its influence on the maturation of dendritic cells. *The Journal of Immunology*, 2002, 168: 919–925.

Effect of administration of BCG at the time of priming with HBsAg

All infants were vaccinated with HBV at birth and at 2 and 4 mo of age and received BCG only at birth or at 2 or at 4,5 moths



Immunogenicity and safety of combined intradermal recombinant Hepatitis B with BCG vaccines at birth☆,☆☆

E.F. Carniel[a,1], A.M. Morcillo[a,1], M.H. Blotta[b,2], M.T.N. Da Silva[a,3], T.N. Mazzola[a,4], M.A.R.G.M. Antonio[a,1], M.L. Zanolli[a,1], A. Aranha Netto[a,1], H.G. Higashi[c,5], I. Raw[c,5], M.M.S. Vilela[a,*]

Summary This randomized, prospective, non-inferiority study aimed to quantify anti-HBs titers induced by recombinant Hepatitis B vaccine from healthy infants vaccinated with combined Hepatitis B and Bacillus Calmette-Guérin (BCG) vaccines (HbsAg 10 μg plus BCG suspension 0.1 mg) and compare them to titers obtained with separated vaccines.
Infants were immunized at birth either with combined intradermal (ID) BCG and Hepatitis B or ID BCG alone and intramuscular (IM) Hepatitis B. Both groups received IM Hepatitis B at 1 and 6 months of age. After the third dose anti-HBs titers ≥10 IU/mL were observed in 99% of vaccinees and ≥1000 IU/mL in 71%. There were no adverse events in both groups. Combination of HbsAg with BCG as first dose did not modify the profile of the humoral immune response for Hepatitis B indicating safety and immunogenicity of this vaccine in newborn.

A. BCG (id) + HBsAg (im) priming at same time
B. Combined BCG-HBsAg (id) priming

Vaccine (2008) 26, 647–652

Co-formulation of BCG and rHBsAg

- Development of vaccine specific for Hepatitis B and tuberculosis by a co-formulation of BCG and recombinant HBsAg where BCG has also an adjuvant role.
- The use of this vaccine is intended for paediatric use in countries where vaccination against tuberculosis and hepatitis B are, or should be, planned during the first day of life.