Curso de Farmácia
Disciplina 0420136 – Integrado MIP (Noturno)

Vacinas

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Departamento de Imunologia
Instituto de Ciências Biomédicas
Universidade de São Paulo

Tópicos Essenciais da Aula

1. **Conhecer aspectos históricos das vacinas.**

2. **Quais são os tipos de vacinas disponíveis?**

3. **Movimento anti-vacina…**

Varíola

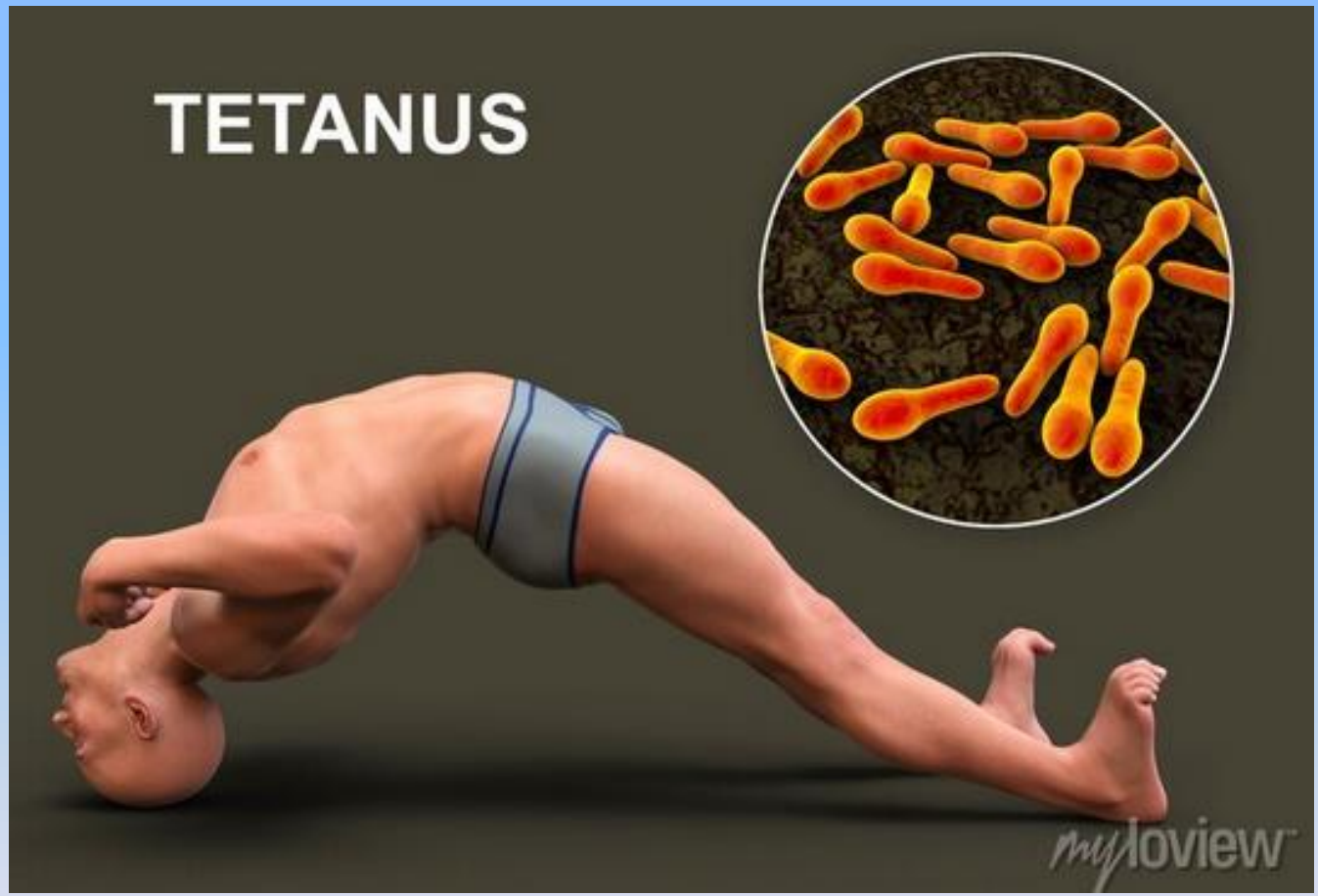
https://www.economist.com/1843/2019/08/30/the-original-anti-vaxxers

Poliomielite

https://www.premiumtimesng.com/news/headlines/561605-polio-cases-drop-by-99-9-who.html

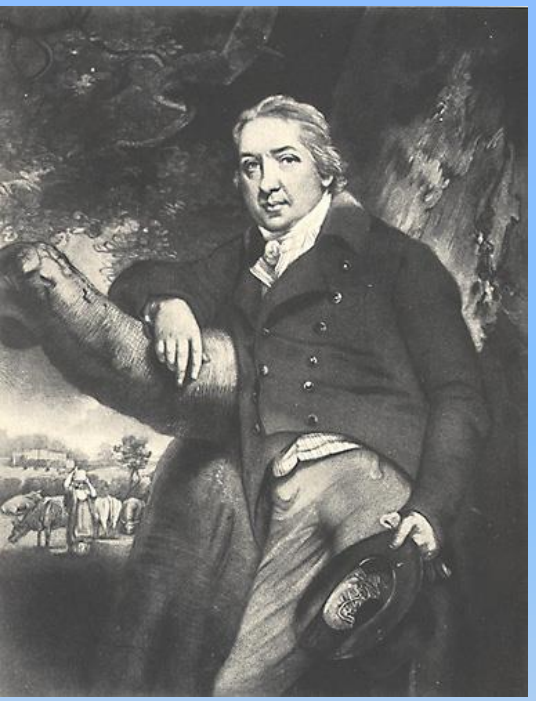
Tétano

https://fineartamerica.com/featured/baby-with-tetanus-dr-ma-ansaryscience-photo-library.html



https://myloview.com.br/quadro-opisthotonus-in-a-man-suffering-from-tetanus-no-128DB8A4

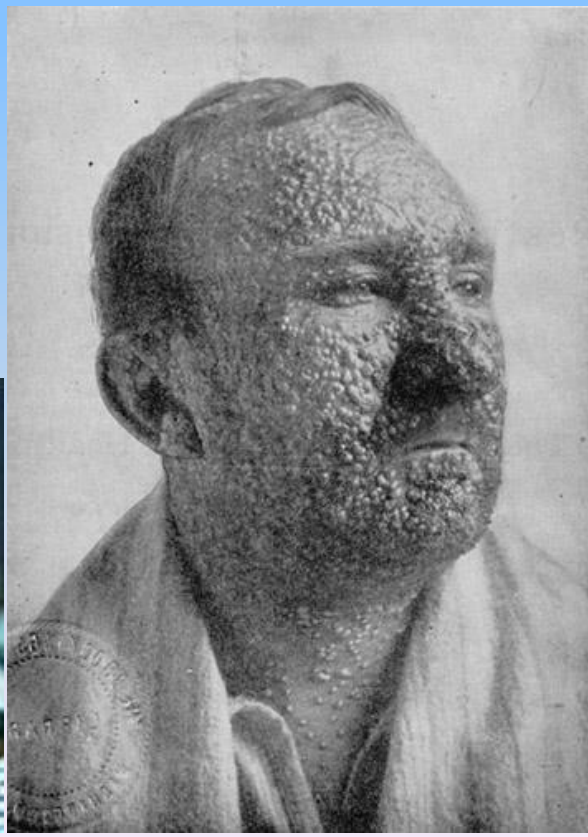
Edward Jenner (1749-1823)



http://www.mytimemachine.co.uk/jenner.htm

Varíola humana (smallpox): grave problema de saúde pública

- ***1/3 dos infectados morriam***
- ***sobreviventes desfigurados***



http://www.bizarremedical.com/things-you-didnt-know-about-smallpox/

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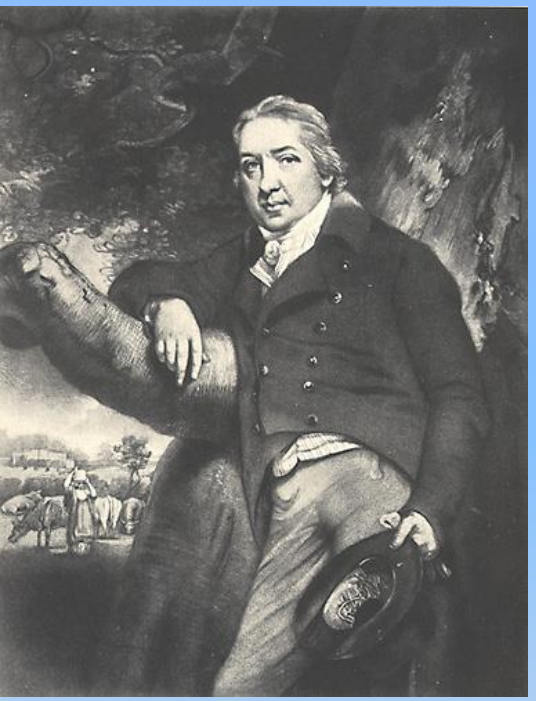

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Varíola bovina (cowpox):

- ***ordenhadeiras tinham uma versão branda***
- ***pus das feridas no úbere foi usado***

http://bioexchange.blogspot.com/2014/04/historia-viva-vacas-e-vacinas.html

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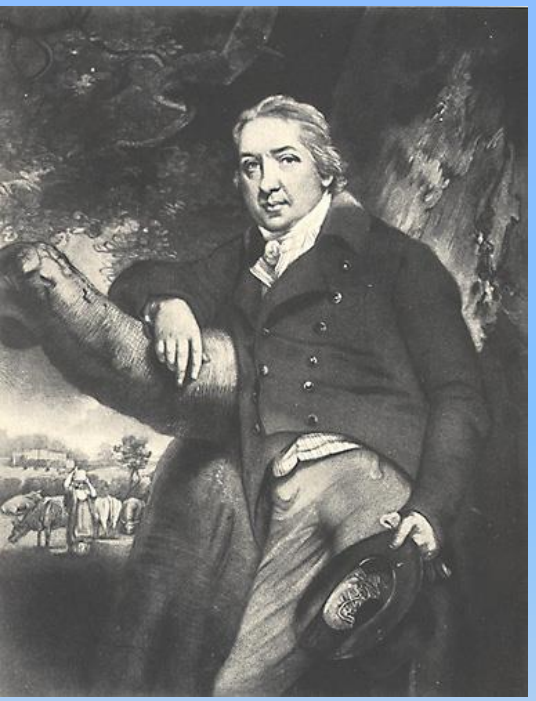

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Vacca: latim para "vaca"

- ***Vaccinius: derivado das vacas***
- ***Vaccination = Vacinação***

➢ ***Vacinação de James Phipps***

http://www.med.umich.edu/opm/newspage/2007/paintings.htm

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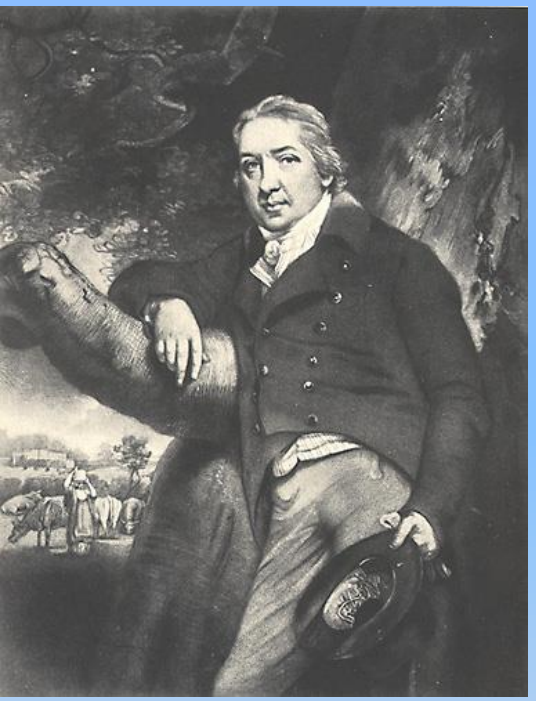

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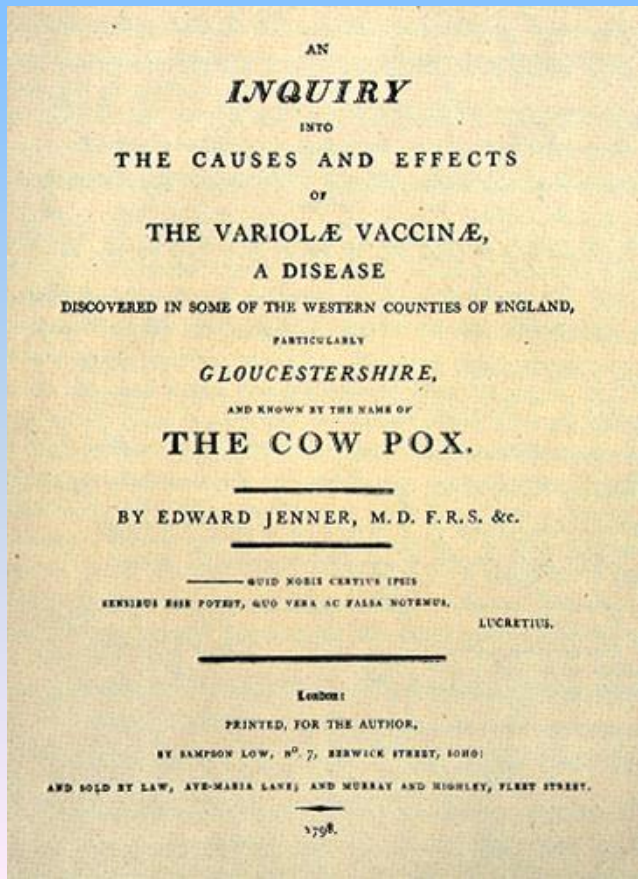

AN

INQUIRY

INTO

THE CAUSES AND EFFECTS

OF

THE VARIOLÆ VACCINÆ,

A DISEASE

DISCOVERED IN SOME OF THE WESTERN COUNTIES OF ENGLAND,

PARTICULARLY

GLOUCESTERSHIRE,

AND KNOWN BY THE NAME OF

THE COW POX.

BY EDWARD JENNER, M.D. F.R.S. &c.

——— QUID NOBIS CERTIUS IPSIS
SENSIBUS HISCE POTEST, QUO VERA AC FALSA NOTEMUS.
LUCRETIUS.

London:

PRINTED, FOR THE AUTHOR,

BY SAMPSON LOW, N°. 7, BERWICK STREET, SOHO:

AND SOLD BY LAW, AVE-MARIA LANE; AND MURRAY AND HIGHLEY, FLEET STREET.

1798.

- *Erradicação da Varíola em 1979 (OMS)*

- *Algumas cepas permanecem estocadas nos EUA e na Rússia*

Emil Adolf von Behring (1854-1917)

- **Filtrados de cultura de *Corynebacterium diphtheriae:***
  - **bacilo diftérico (bactéria Gram positiva)**
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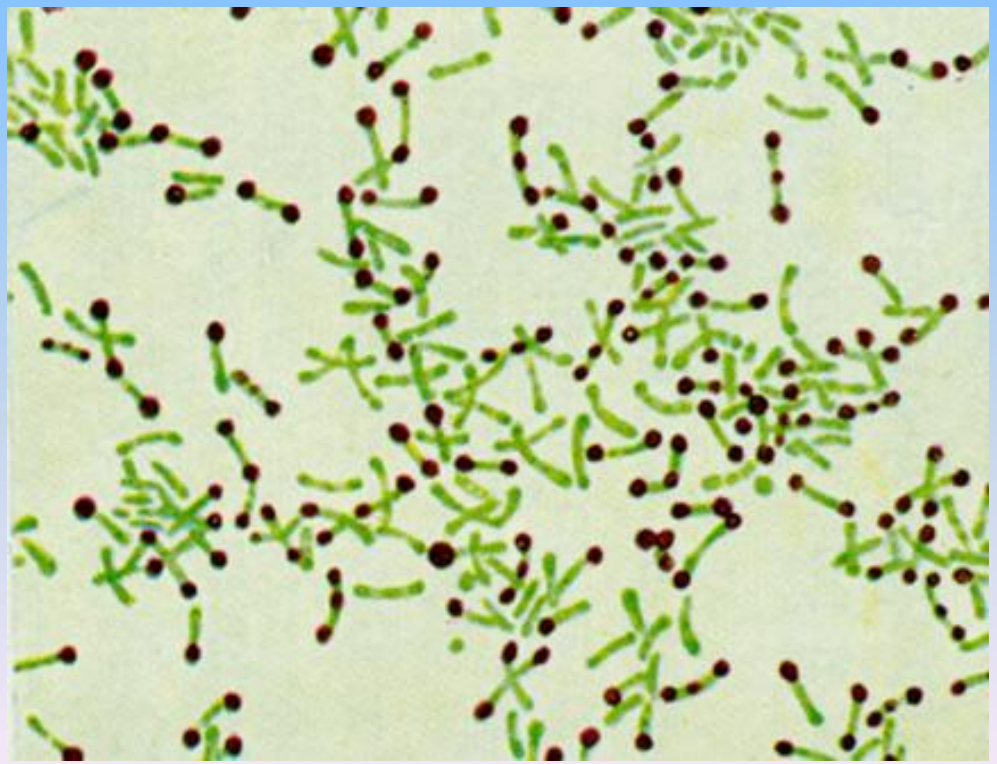

http://textbookofbacteriology.net/diphtheria.html

http://nobelprize.org/nobel_prizes/medicine/laureates/1901/

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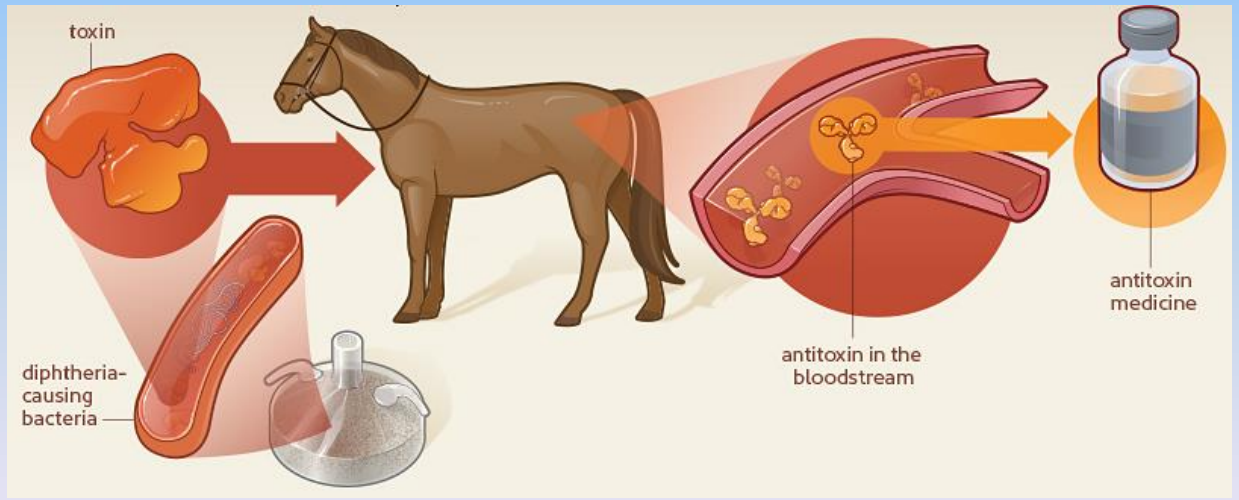
  - **antitoxinas = proteção**



https://www.nlm.nih.gov/exhibition/fromdnatobeer/exhibition-interactive/illustrations/diphtheria-alternative.html

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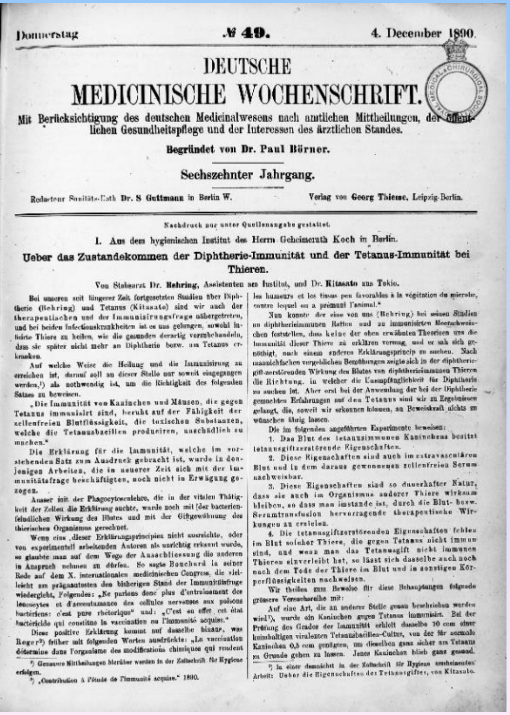
  - antitoxinas = proteção

- Soro de animais contendo antitoxina transferem proteção
  - soro anti-diftérico
  - criou uma companía e ficou rico



Donnerstag | № 49. | 4. December 1890.

DEUTSCHE
MEDICINISCHE WOCHENSCHRIFT.

Mit Berücksichtigung des deutschen Medicinalwesens nach amtlichen Mittheilungen, der öffentlichen Gesundheitspflege und der Interessen des ärztlichen Standes.

Begründet von Dr. Paul Börner.

Sechszehnter Jahrgang.

Redacteur Sanitäts-Rath Dr. S. Guttmann in Berlin W. — Verlag von Georg Thieme, Leipzig-Berlin.

Nachdruck nur unter Quellenangabe gestattet.

I. Aus dem hygienischen Institut des Herrn Geheimerath Koch in Berlin.

Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren.

Von Stabsarzt Dr. Behring, Assistenten am Institut, und Dr. Kitasato aus Tokio.

Bei unseren seit längerer Zeit fortgesetzten Studien über Diphtherie (Behring) und Tetanus (Kitasato) sind wir auch der therapeutischen und der Immunisirungsfrage nähergetreten, und bei beiden Infectionskrankheiten ist es uns gelungen, sowohl inficirte Thiere zu heilen, wie die gesunden derartig vorzubehandeln, dass sie später nicht mehr an Diphtherie bezw. am Tetanus erkranken.

Auf welche Weise die Heilung und die Immunisirung zu erreichen ist, darauf soll an dieser Stelle nur soweit eingegangen werden,[1] als nothwendig ist, um die Richtigkeit des folgenden Satzes zu beweisen.

„Die Immunität von Kaninchen und Mäusen, die gegen Tetanus immunisirt sind, beruht auf der Fähigkeit der zellenfreien Blutflüssigkeit, die toxischen Substanzen, welche die Tetanusbacillen produciren, unschädlich zu machen.“

Die Erklärung für die Immunität, welche im vorstehenden Satz zum Ausdruck gebracht ist, wurde in denjenigen Arbeiten, die in neuerer Zeit sich mit der Immunitätsfrage beschäftigten, noch nicht in Erwägung gezogen.

Ausser mit der Phagocytenlehre, die in der vitalen Thätigkeit der Zellen die Erklärung suchte, wurde noch mit der bacterienfeindlichen Wirkung des Blutes und mit der Giftgewöhnung des thierischen Organismus gerechnet.

Wenn eins dieser Erklärungsprincipien nicht ausreichte, oder von experimentell arbeitenden Autoren als unrichtig erkannt wurde, so glaubte man auf dem Wege der Ausschliessung die anderen in Anspruch nehmen zu dürfen. So sagte Bouchard in seiner Rede auf dem X. internationalen medicinischen Congress, die vielleicht am prägnantesten den bisherigen Stand der Immunitätsfrage wiedergiebt, Folgendes: „Ne parlons donc plus d'entrainement des leucocytes et d'accoutumance des cellules nerveuses aux poisons bactériens: c'est pure rhétorique“ und: „C'est en effet cet état bactéricide qui constitue la vaccination ou l'immunité acquise.“

Diese positive Erklärung kommt auf dasselbe hinaus, was Roger[2] früher mit folgenden Worten ausdrückte: „La vaccination détermine dans l'organisme des modifications chimiques qui rendent les humeurs et les tissus peu favorables à la végétation du microbe, contre lequel on a prémuni l'animal.“

Nun konnte der eine von uns (Behring) bei seinen Studien an diphtherieimmunen Ratten und an immunisirten Meerschweinchen feststellen, dass keine der oben erwähnten Theorieen uns die Immunität dieser Thiere zu erklären vermag, und er sah sich genöthigt, nach einem anderen Erklärungsprincip zu suchen. Nach mannichfachen vergeblichen Bemühungen zeigte sich in der diphtheriegift-zerstörenden Wirkung des Blutes von diphtherieimmunen Thieren die Richtung, in welcher die Unempfänglichkeit für Diphtherie zu suchen ist. Aber erst bei der Anwendung der bei der Diphtherie gemachten Erfahrungen auf den Tetanus sind wir zu Ergebnissen gelangt, die, soweit wir erkennen können, an Beweiskraft nichts zu wünschen übrig lassen.

Die im folgenden angeführten Experimente beweisen:

1. Das Blut des tetanusimmunen Kaninchens besitzt tetanusgiftzerstörende Eigenschaften.
2. Diese Eigenschaften sind auch im extravasculären Blut und in dem daraus gewonnenen zellenfreien Serum nachweisbar.
3. Diese Eigenschaften sind so dauerhafter Natur, dass sie auch im Organismus anderer Thiere wirksam bleiben, so dass man imstande ist, durch die Blut- bezw. Serumtransfusion hervorragende therapeutische Wirkungen zu erzielen.
4. Die tetanusgiftzerstörenden Eigenschaften fehlen im Blut solcher Thiere, die gegen Tetanus nicht immun sind, und wenn man das Tetanusgift nicht immunen Thieren einverleibt hat, so lässt sich dasselbe auch noch nach dem Tode der Thiere im Blut und in sonstigen Körperflüssigkeiten nachweisen.

Wir theilen zum Beweise für diese Behauptungen folgende grössere Versuchsreihe mit:

Auf eine Art, die an anderer Stelle genau beschrieben werden wird[1], wurde ein Kaninchen gegen Tetanus immunisirt. Bei der Prüfung des Grades der Immunität erhielt dasselbe 10 ccm einer keimhaltigen virulenten Tetanusbacillen-Cultur, von der für normale Kaninchen 0,5 ccm genügten, um dieselben ganz sicher am Tetanus zu Grunde gehen zu lassen. Jenes Kaninchen blieb ganz gesund.

[1] Genauere Mittheilungen hierüber werden in der Zeitschrift für Hygiene erfolgen.

[2] „Contribution à l'étude de l'immunité acquise.“ 1890.

[1] In einer demnächst in der Zeitschrift für Hygiene erscheinenden Arbeit: Ueber die Eigenschaften des Tetanusgiftes, von Kitasato.

https://en.wikipedia.org/wiki/Antitoxin

Frasco de 1895

http://nobelprize.org/nobel_prizes/medicine/laureates/1901/

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- **Soro de animais contendo antitoxina transferem proteção**
  - **soro anti-diftérico**
  - **criou uma compania e ficou rico**

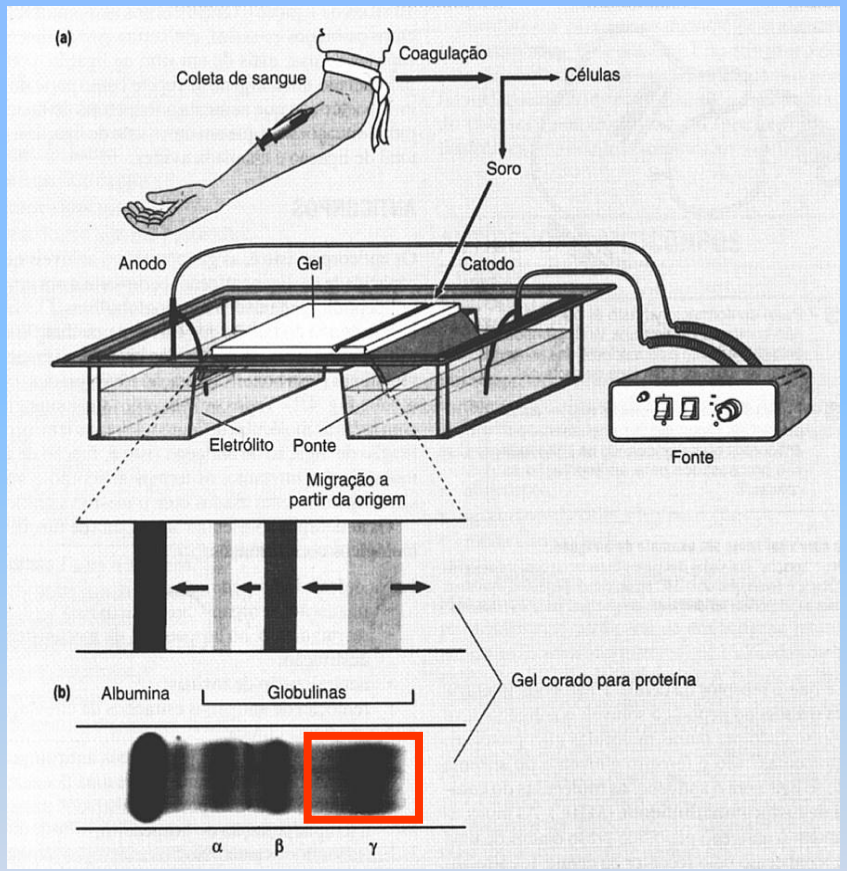
- **Foi laureado com o 1º Prêmio Nobel**

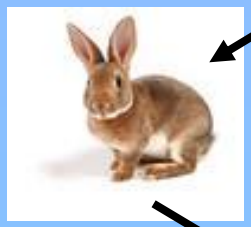
The Nobel Prize in Physiology or Medicine 1901

"for his work on serum therapy, especially its application against diphtheria, by which he has opened a new road in the domain of medical science and thereby placed in the hands of the physician a victorious weapon against illness and deaths"

http://nobelprize.org/nobel_prizes/medicine/laureates/1901/

Técnica de Eletroforese

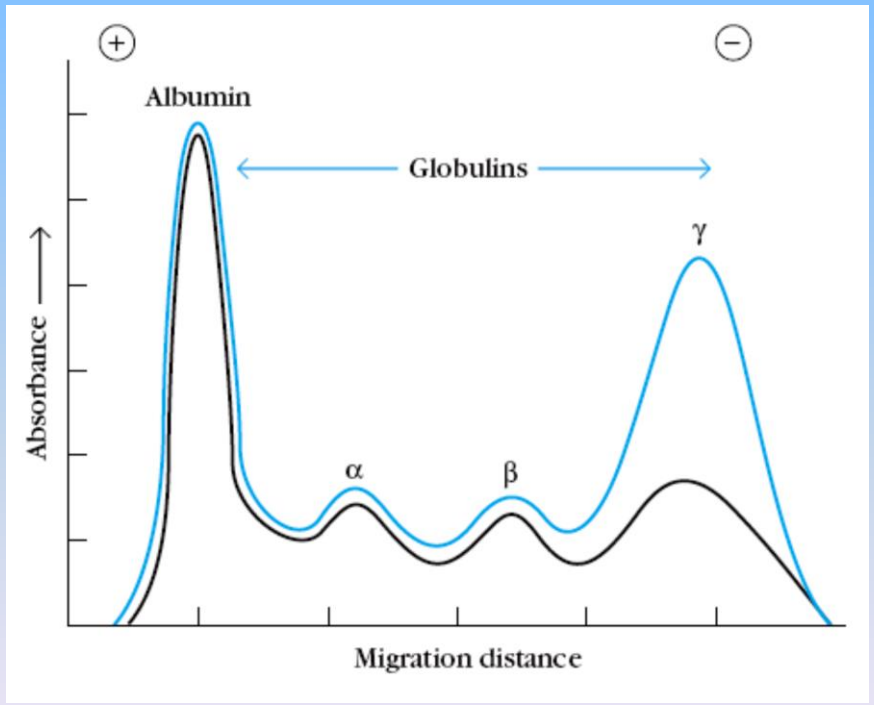




OVA ou veículo

Soro

Soro +OVA



- γ-globulinas (gamaglobulinas)
- imunoglobulinas
- anticorpos

Arne Tiselius & Elvin Kabat
The Journal of Experimental Medicine, 1939

Isotipos/Classes de Imunoglobulinas

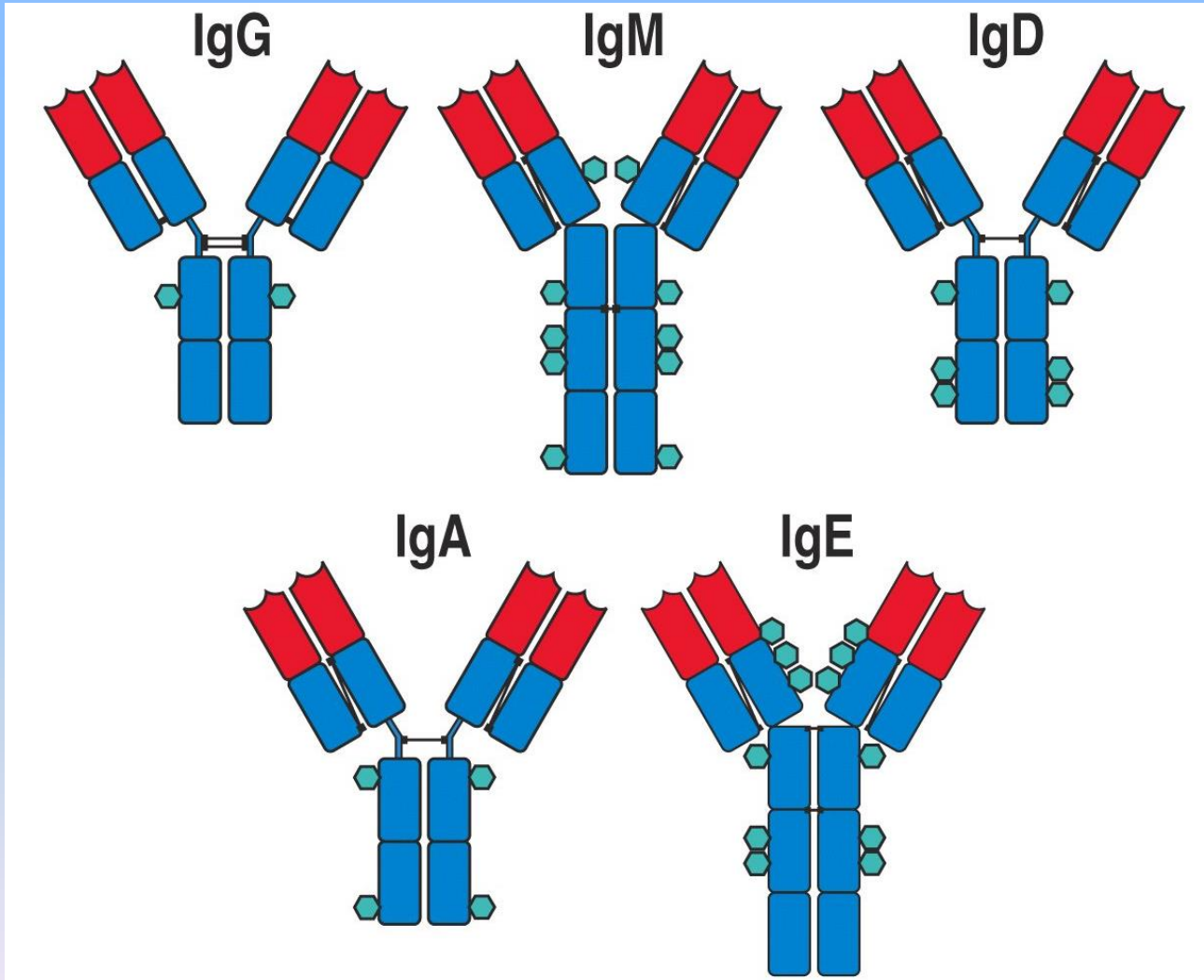


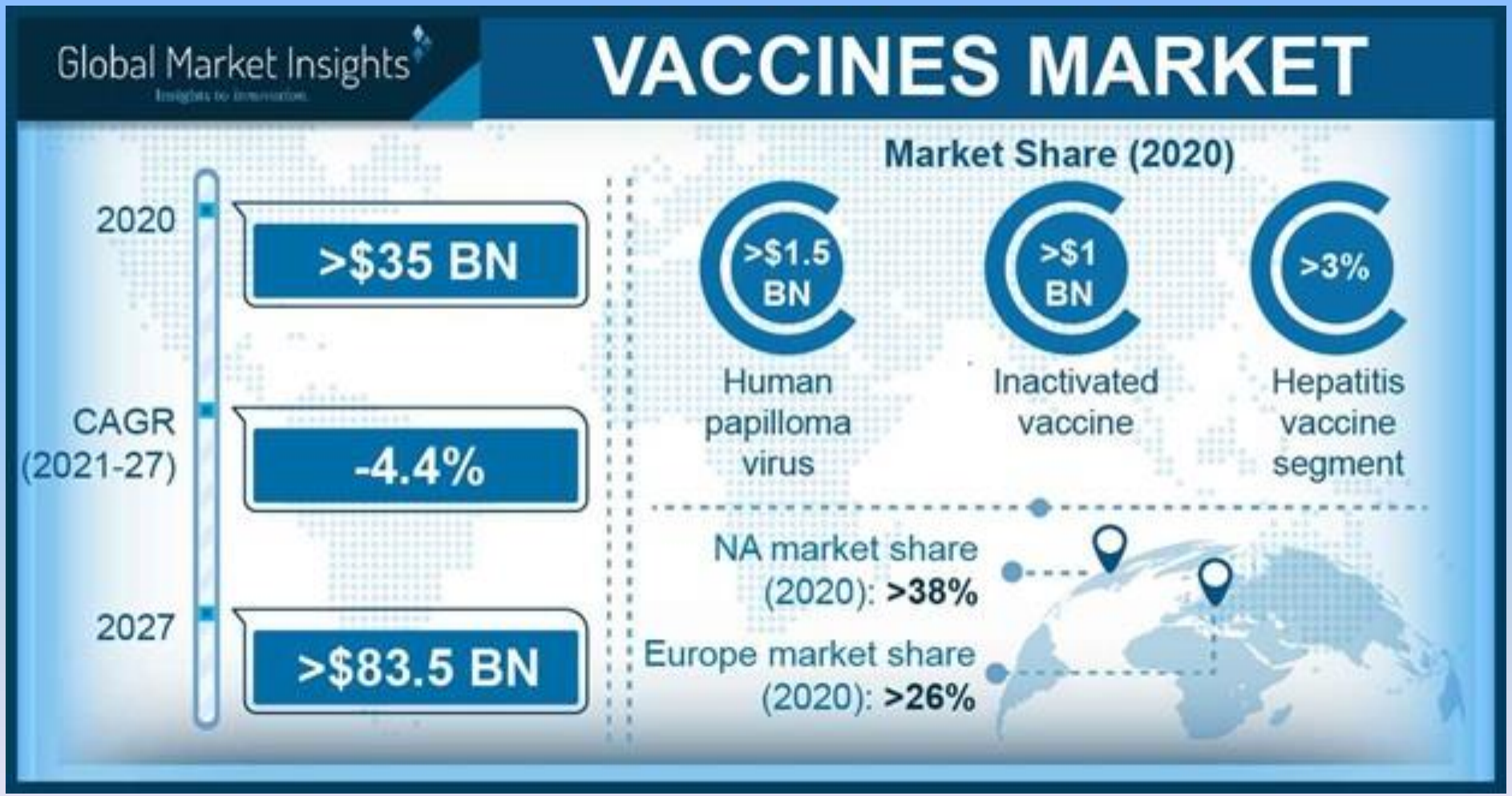
Figure 4-18 Immunobiology, 6/e. (© Garland Science 2005)

Eficácia da Vacinação

Disease	Maximum Number of Cases (Year)	Number of Cases in 2018	Percentage Change
Diphtheria	206,939 (1921)	1	–99.99
Measles	894,134 (1941)	375	–99.95
Mumps	152,209 (1968)	2,515	–95.82
Pertussis	265,269 (1934)	15, 609	–94.11
Polio (paralytic)	21,269 (1952)	0	–100.0
Rubella	57,686 (1969)	4	–99.99
Tetanus	1,560 (1923)	23	–98.52
Haemophilus influenzae type B	~20,000 (1984)	38	–99.83
Hepatitis B	26,611 (1985)	3,322	–87.51

Abbas, Lichtman, Pillai, 10ª Edition, 2022.

Mercado de Vacinas no Mundo (2020)



https://www.gminsights.com/industry-analysis/vaccines-market

Mercado de Vacinas no Mundo (2021)

https://www.gminsights.com/industry-analysis/vaccines-market

Tipos de Vacinas

1- Microrganismos vivos atenuados

doença		considerações
vírus	poliomielite sabin	tipos 2 e 3 podem reverter a virulência; também vacina inativada
	sarampo	80% de eficácia
	caxumba	
	rubéola	atualmente fornecida a ambos os sexos
	febre amarela	estável desde 1937
	varicela-zóster	principalmente em leucemias
	hepatite A	também vacina inativada
bactéria	tuberculose	estável desde 1921; alguma proteção também contra hanseníase

Adaptado de: Male, Imunologia, 8ª Edição, 2014.

Tipos de Vacinas

1- Microrganismos vivos atenuados

- ***Prós:***

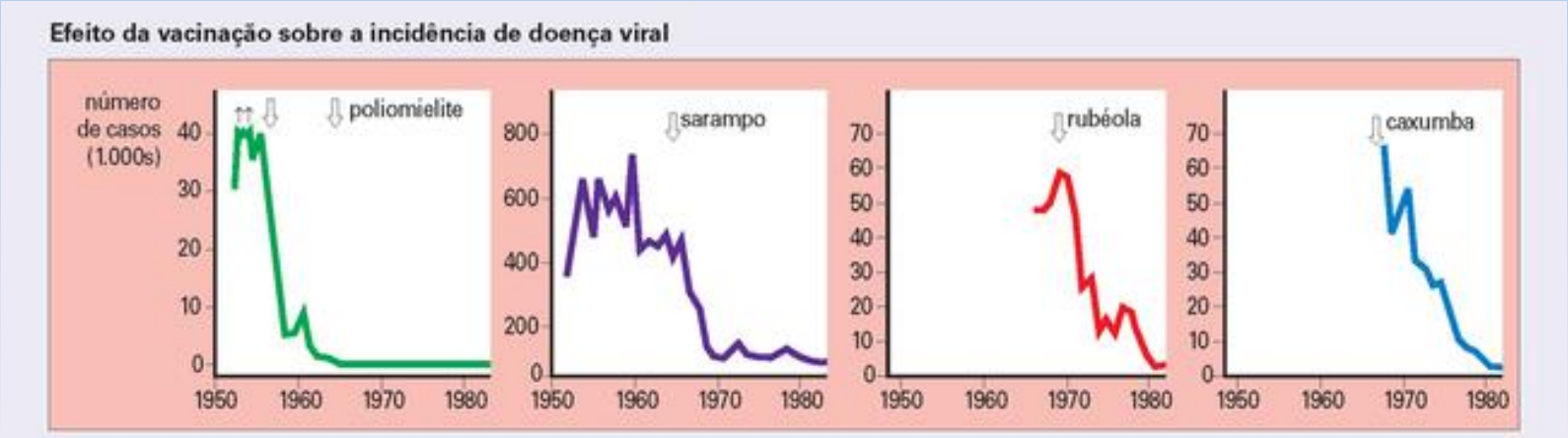
  - induz resposta parecida com a infecção natural

- ***Contras:***

  - transporte e estocagem

  - indivíduos imunocomprometidos podem desenvolver a doença

  - mutações que revertam a virulência



Male, Imunologia, 8ª Edição, 2014.

Tipos de Vacinas

2- Microrganismos inativados (organismo inteiro)

doença		considerações
vírus	poliomielite Salk	preferida na Escandinávia; segura para pacientes imunocomprometidos
	raiva	pode ser administrada após-exposição, com antissoro passivo
	influenza	cepa-específica
	hepatite A	também vacina atenuada
bactéria	coqueluche	dano cerebral em casos raros? substituída por vacina acelular, que é mais segura
	febre tifoide	cerca de 70% de proteção
	cólera	combinada com toxina modificada recombinante
	peste	apenas proteção de curta duração
	febre Q	boa proteção

Adaptado de: Male, Imunologia, 8ª Edição, 2014.

Tipos de Vacinas

2- Microrganismos inativados (organismo inteiro)

- ***Prós:***
  - ***- estabilidade***
  - ***- impossibilidade de reversão***
  - ***- boa resposta das células T $CD4^+$***
- ***Contras:***
  - ***- doses de reforço***
  - ***- adjuvantes***

Tipos de Vacinas

3- Subunidades/Toxoides

Vacinas de subunidade

	organismo	considerações
vírus	vírus da hepatite B	antígeno de superfície pode ser purificado a partir do sangue de portadores ou produzido em leveduras por tecnologia de DNA recombinante
bactéria	*Neisseria meningitidis*	polissacarídeos capsulares ou conjugados dos grupos A, C, γ e W-135 são eficazes grupo B não é imunogênico
	Streptococcus pneumoniae	84 sorótipos: vacinas do polissacarídeo capsular contêm 23 sorótipos; conjugados com cinco ou sete sorótipos bacterianos agora disponíveis
	Haemophilus influenzae B	boas vacinas conjugadas atualmente disponíveis

Male, Imunologia, 8ª Edição, 2014.

Tipos de Vacinas

3- Subunidades/Toxoides

Vacinas baseadas em toxinas

organismo	vacina	considerações
Clostridium tetani	toxina inativada (formalina)	três doses, precipitadas em alúmen; reforço a cada 10 anos
Corynebacterium diphtheriae		geralmente administrada com a vacina contra o tétano
Vibrio cholerae	toxina modificada recombinante	combinada com organismos mortos inteiros
Clostridium perfringens	toxina inativada (formalina)	para ovinos recém-nascidos

Male, Imunologia, 8ª Edição, 2014.

Tipos de Vacinas

3- Subunidades/Toxoides

- *Prós:*
  - *menores efeitos adversos*
  - *possibilidade de conjugações*
- *Contras:*
  - *imunogenicidade relativamente baixa (reforços ao longo da vida)*
  - *altas concentrações de adjuvantes*

Tipos de Vacinas

4- DNA e vetores virais

- ***Vacinas de DNA licenciadas para uso veterinário:***
  - ***Vírus do Nilo Ocidental (WNV) em cavalos***
  - ***Vírus da necrose hematopoiética (VNHI) em salmões***
  - ***Melanoma em canino***
  - ***Necrose pancreática infecciosa em salmões***
  - ***Terapia para liberação hormonal do fator de crescimento em suínos***
  - ***Influenza aviária H5N1 em frangos***

- ***Vacinas de RNA e vetores virais: SARS-CoV-2***

Tipos de Vacinas

4- DNA e vetores virais

- ***Prós:***

  - flexibilidade: vários antígenos, facilmente modificada

  - baixo custo (rápida de produzir e alterar, larga escala)

  - estabilidade e segurança (estocagem e ausência de reversão)

  - respostas humoral (anticorpos) e celular (T $CD4^+$ e T $CD8^+$)

- ***Contras:***

  - riscos da manipulação genética

  - possibilidade de integração ao DNA celular (vacinas de DNA)

  - limitada a antígenos proteicos

  - respostas contra os vetores afeta eficiência (?)

  - possibilidade de tolerância (produção endógena)

  - risco de doença autoimmune (anticorpos anti-DNA) (?)

Mercado Global de Vacinas

The market is projected to witness moderate growth during next **five years**

Dominance in the market

MARKET DYNAMICS & SEGMENTS

BY TECHNOLOGY

- **Conjugate Vaccines**
- Inactivated and Subunit Vaccines
- Live Attenuated Vaccines
- Recombinant Vaccines
- Toxoid Vaccines
- Others

BY PATIENT TYPE

- **Paediatric**
- Adult

BY REGION

- **North America**
- Asia Pacific
- Europe
- Latin America
- Middle East and Africa

BY END USE

- **Hospitals**
- Clinics
- Vaccination Centres
- Academic and Research Institutes
- Others

BY PRODUCT TYPE

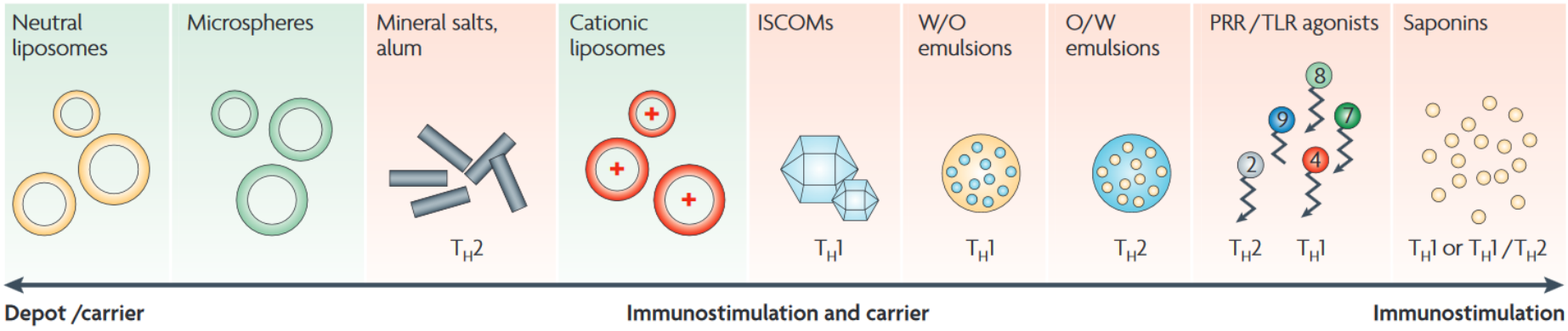
- **Multivalent Vaccine**
- Monovalent Vaccine

https://ipsnews.net/business/2021/03/04/vaccine-market-research-report-2020-global-industry-manufacturer-size-share-trends-and-forecast-by-2025/

Adjuvantes

Propriedades

- ***Carreamento/depósito***
- ***Imunoestimulação***
- ***Imunomodulação***



Guy, Nat. Rev. Microbiol., v. 5, p. 505-517, 2007

Adjuvantes

tipo de adjuvante	rotineiramente utilizado em humanos	experimental* ou muito tóxico para uso em humanos†
sais inorgânicos	hidróxido de alumínio (Alhydrogel®) fosfato de alumínio fosfato de cálcio	hidróxido de berílio
sistemas de liberação		lipossomos* ISCOMs* polímeros em blocos formulações de liberação lenta*
produtos bacterianos	*Bordetella pertussis* (com toxoides diftéricos e tetânicos)	BCG *Mycobacterium bovis* e óleo† (adjuvante completo de Freund) muramil dipeptídeo (MDP)† CpG
mediadores naturais (citocinas)		IL-1 IL-2 IL-12 IFNγ

ISCOMs, complexos imunoestimulantes

Male, Imunologia, 8ª Edição, 2014.

Calendário Vacinal (Nascimento aos 6 anos)

https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/c/calendario-de-vacinacao

Calendário Vacinal (7 aos 9 anos e adolescentes)

CALENDÁRIO VACINAL

DOS 7 AOS 9 ANOS
E ADOLESCENTES

MENINAS ENTRE 9 E 14 ANOS

HPV (duas doses com intervalo de 6 meses entre elas)

MENINOS ENTRE 11 E 14 ANOS

HPV (duas doses com intervalo de 6 meses entre elas)

MENINAS E MENINOS ENTRE 11 E 14 ANOS

Meningocócica C (dose única ou reforço dependendo da situação vacinal)

QUALQUER IDADE

VIP
(3 doses dependendo da situação vacinal)

BCG
(dependendo da situação vacinal, prioritariamente até 15 anos)

Febre Amarela
(dose única se nunca tiver tomado);

Hepatite B
(3 doses dependendo da situação vacinal);

Dupla adulto
(3 doses dependendo da situação vacinal e reforço a cada 10 anos);

Tríplice viral
(2 doses dependendo da situação vacinal).

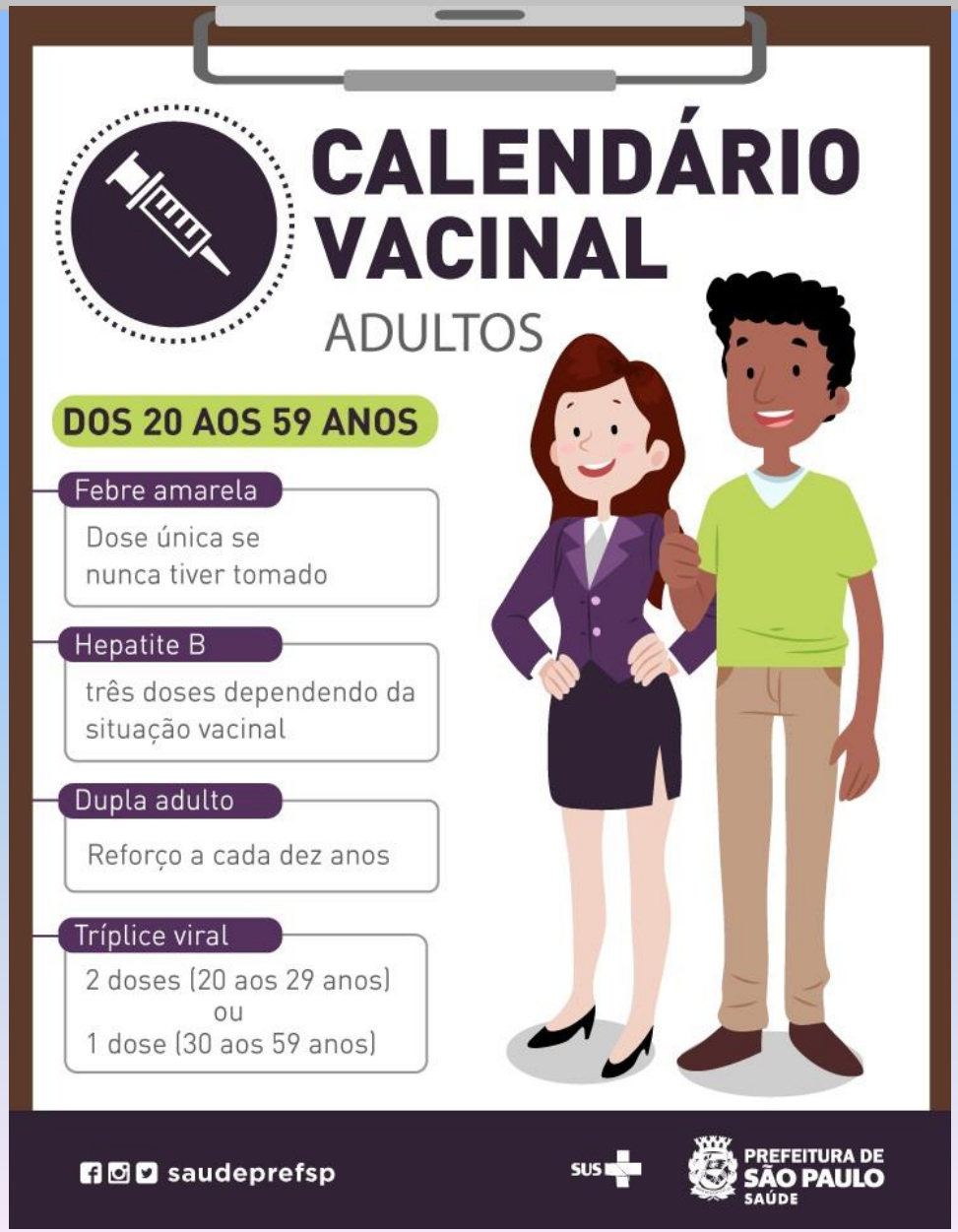
saudeprefsp

SUS

PREFEITURA DE SÃO PAULO
SAÚDE

https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/c/calendario-de-vacinacao

Calendário Vacinal (20 aos 59 anos)



https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/c/calendario-de-vacinacao

Calendário Vacinal (60 anos ou mais)

CALENDÁRIO VACINAL
IDOSOS - 60 ANOS OU MAIS

60 ANOS OU MAIS

Febre Amarela
(Dose única, se nunca tiver vacinado.
Só deve ser tomada após avaliação e autorização de profissional de saúde)

Hepatite B
(3 doses, dependendo da situação vacinal)

Dupla Adulto
(reforço a cada 10 anos)

Pneumocócica 23 Valente
(indicada para públicos-alvos específicos, dependendo da condição clínica)

minsaude

https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/c/calendario-de-vacinacao

Controvérsia: vacinas e autismo

https://www.forbes.com/sites/kavinsenapathy/2016/03/28/no-andrew-wakefield-youre-not-being-censored-and-you-dont-deserve-due-process/#69a5dc3a297a

Dr. Andrew J. Wakerfield

- ***Publicou artigos associando o vírus do sarampo com a Doença de Crohn***
- ***Posteriormente associou a doença à vacina contra o sarampo***
- ***Grupo de especialistas britânicos revisaram artigos na área em 1998 e não confirmaram essa hipótese***

- ***Publicou artigo no <u>The Lancet</u> sobre 12 crianças com autismo, sendo que em 8 delas descreveram uma síndrome chamada enterocolite autística, associando enteropatias, autismo e a vacina MMR (sarampo, caxumba e rubéola)***
- ***Estudos independentes nunca confirmaram essa relação. Como o autor se recusou a incluir controles no seu estudo, o artigo foi retratado***

EARLY REPORT

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Findings Onset of behavioural symptoms was associated by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in another. All 12 children had intestinal abnormalities, ranging from lymphoid nodular hyperplasia to aphthoid ulceration. Histology showed patchy chronic inflammation in 11 children and reactive ileal lymphoid hyperplasia in seven, but no granulomas. Behavioural disorders included autism (nine), disintegrative psychosis (one), and possible postviral or vaccinal encephalitis (two). There were no focal neurological abnormalities and MRI and EEG tests were normal. Abnormal laboratory results were significantly raised urinary methylmalonic acid compared with age-matched controls ($p=0.003$), low haemoglobin in four children, and a low serum IgA in four children.

Interpretation We identified associated gastrointestinal disease and developmental regression in a group of previously normal children, which was generally associated in time with possible environmental triggers.

Lancet 1998; **351**: 637–41
See Commentary page

Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology (A J Wakefield FRCS, A Anthony MB, J Linnell PhD, A P Dhillon MRCPath, S E Davies MRCPath) **and the University Departments of Paediatric Gastroenterology** (S H Murch MB, D M Casson MRCP, M Malik MRCP, M A Thomson FRCP, J A Walker-Smith FRCP), **Child and Adolescent Psychiatry** (M Berelowitz FRCPsych), **Neurology** (P Harvey FRCP), **and Radiology** (A Valentine FRCR), **Royal Free Hospital and School of Medicine, London NW3 2QG, UK**

Correspondence to: Dr A J Wakefield

Introduction

We saw several children who, after a period of apparent normality, lost acquired skills, including communication. They all had gastrointestinal symptoms, including abdominal pain, diarrhoea, and bloating and, in some cases, food intolerance. We describe the clinical findings, and gastrointestinal features of these children.

Patients and methods

12 children, consecutively referred to the department of paediatric gastroenterology with a history of a pervasive developmental disorder with loss of acquired skills and intestinal symptoms (diarrhoea, abdominal pain, bloating and food intolerance), were investigated. All children were admitted to the ward for a week, accompanied by their parents.

Clinical investigations

We took histories, including details of immunisations and exposure to infectious diseases, and assessed the children. In 11 cases the history was obtained by the senior clinician (JW-S). Neurological and psychiatric assessments were done by consultant staff (PH, MB) with HMS-4 criteria.[1] Developmental assessment included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MAT under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRI), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

Laboratory investigations

Thyroid function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known causes of childhood neurodegenerative disease. Urinary methylmalonic acid was measured in random urine samples from eight of the 12 children and 14 age-matched and sex-matched normal controls, by a modification of a technique described previously.[2] Chromatograms were scanned digitally on computer, to analyse the methylmalonic-acid zones from cases and controls. Urinary methylmalonic-acid concentrations in patients and controls were compared by a two-sample *t* test. Urinary creatinine was estimated by routine spectrophotometric assay.

Children were screened for anticndomysial antibodies and boys were screened for fragile-X if this had not been done

RETRACTED

Wakefield et al., The Lancet, v. 351, p. 637-641, 1998

Necessidade de Monitoramento e Controle de Qualidade Constantes

Problemas relacionados à segurança vacinal

tipo de vacina	possíveis problemas de segurança	exemplos
vacinas atenuadas	reversão para o tipo virulento	principalmente poliomielite tipos 2 e 3
	doença grave em pacientes imunossuprimidos	vacínia, BCG, sarampo
	infecção persistente	varicela-zóster
	hipersensibilidade aos antígenos virais	sarampo
	hipersensibilidade aos antígenos do ovo	sarampo, caxumba
vacinas inativadas	vacina não inativada	acidentes com poliomielite no passado
	contaminação por fungos	hepatite B
	contaminação por vírus animal	poliomielite
	contaminação por endotoxina	coqueluche

Male, Imunologia, 8ª Edição, 2014.

Movimento Anti-Vacinas

https://www.economist.com/1843/2019/08/30/the-original-anti-vaxxers

Movimento Anti-Vacinas

https://www.rollingstone.com/culture/culture-features/celebrities-anti-vaxxers-jessica-biel-847779/