XXI sajandi vaktsiinid

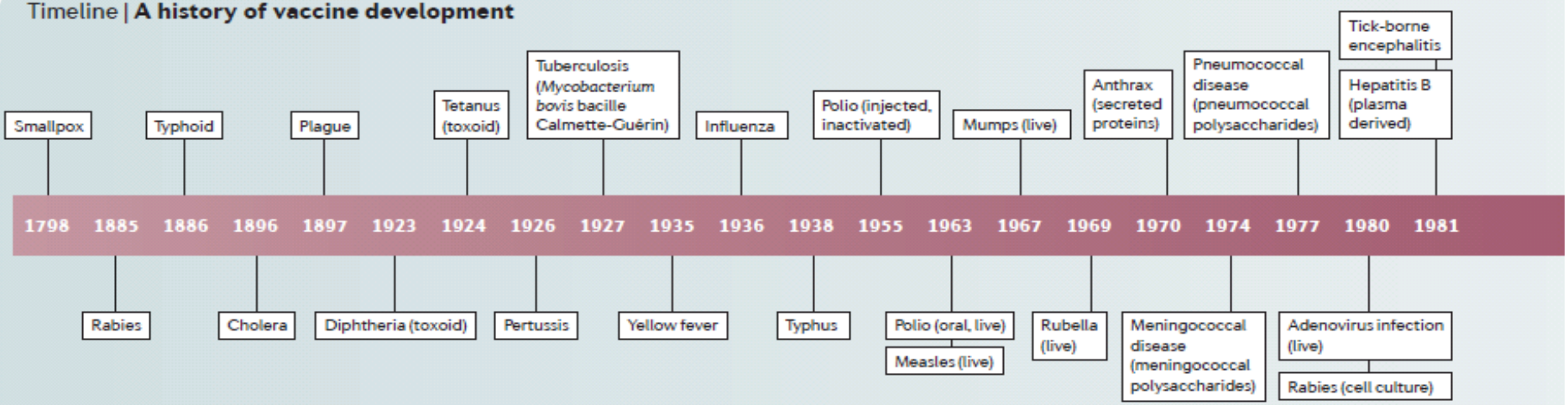
Vaktsineerimise neljas sajand

EAP 2014

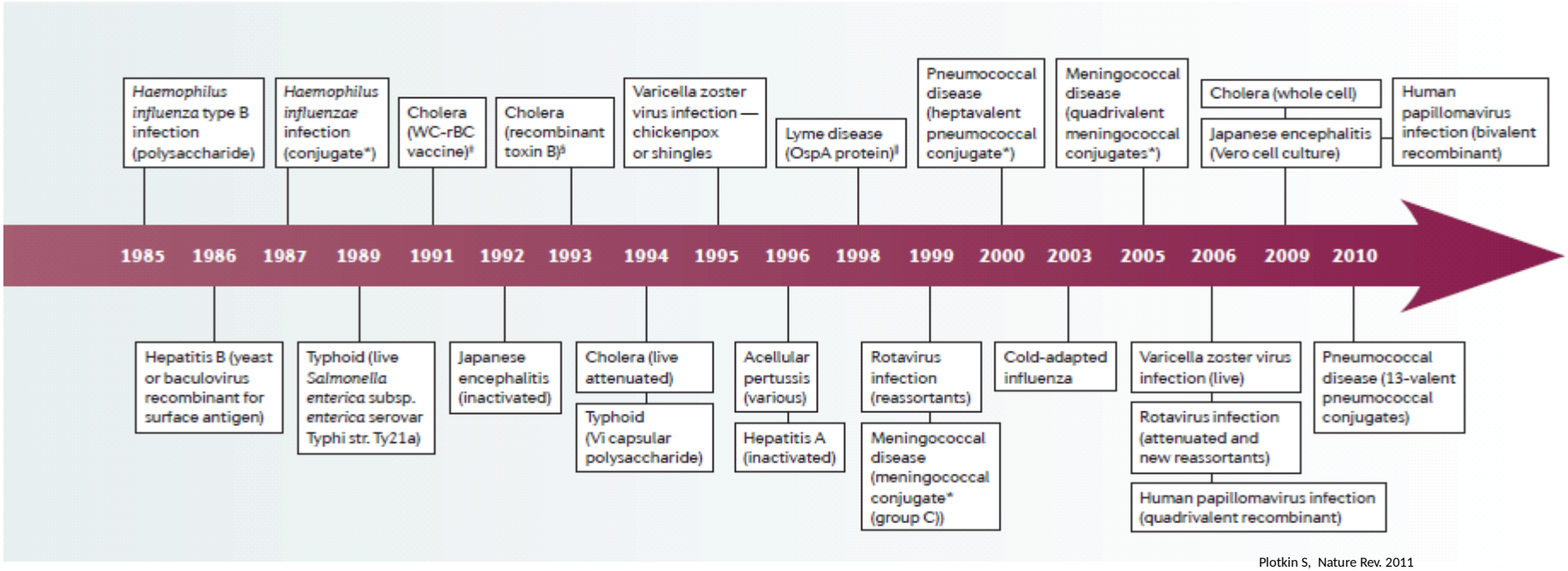
Eda Tamm

SA TÜK Lastekliinik

Timeline | **A history of vaccine development**



*Capsular polysaccharide conjugated to carrier proteins. ‖Killed, recombinant B subunit, whole-cell vaccine. §Cholera toxin B combined with enterotoxigenic *Escherichia coli*. ‖Now withdrawn.



Plotkin S, Nature Rev. 2011

,,Esimese põlvkonna" vaktsiinid

- **18.sajand** – 1796 Edward Jenner – rõugete vastane vaktsineerimine. 1979 –maailm rõugete vaba
- **19.sajand** – 1885 Louis Pasteur – **elus tekitajate nõrgestamine** - marutõve, katku vaktsiinid
- **19/20.sajand** - D.Salmon ja T. Smith - **bakterite inaktiveerimine**, antitoksiinid ja toksoidid- tüüfuse ja koolera vaktsiinid
- **20.sajand 1900-1950** – difteeria toksoid, teetanuse toksoid

Täisrakuline läkaköha vaktsiin- sisaldab inaktiveeritud tervet bakterirakku

Tuberkuloosi vaktsiin (Calmette-Guerin) - avirulentsete *M.bovise* tüvede selekteerimine läbi korduvate passaazide: 230 passaazi söötmes 14 aasta jooksul

Kollapalaviku vaktsiin- viiruse tüvi 17D, korduvad passaazid kanaembrüotel

Gripi vaktsiin – W. Smith – inaktiveeritud vaktsiin, intranasaalne elusvaktsiin

,,Teise põlvkonna“ vaktsiinid ehk vaktsineerimise kuldajastu

20. sajandi keskpaigast - tekitajate kasvatamine koekultuuridel (Enders, Robbins, Weller)

- **50ndad**

Polio (Sabini tüüp)- inaktiveeritud vaktsiin- 1955

Polio (Salk) – elusvaktsiin - 1963

- **60ndad** – 3 klassikalist vaktsiini – leetrite, mumpsi ja punetiste vaktsiinid
- **70ndad** – tuulerõugete vaktsiin

Uued tehnoloogiad

Varasemad tehnoloogiad:

Ei võimaldada arendada välja vaktsiine

- tekitajate suhtes, mis ei kasva *in vitro*

  (papilloomiviirused 16 ja 18)

- millele on iseloomulik suur antigeenne mitmekesisus

  (B-grupi meningokokk, HIV, HCV)

- tekitajate suhtes, mis rakusiseses faasis on kontrollitavad peamisel T-lümfotsüütide poolt.

  (TBC, malaaria)

Traditsiooniliste vaktsiinide arendamine ja tootmine on

liiga pikaajaline protsess, mis ei vasta enam kaasaja

vajadustele.

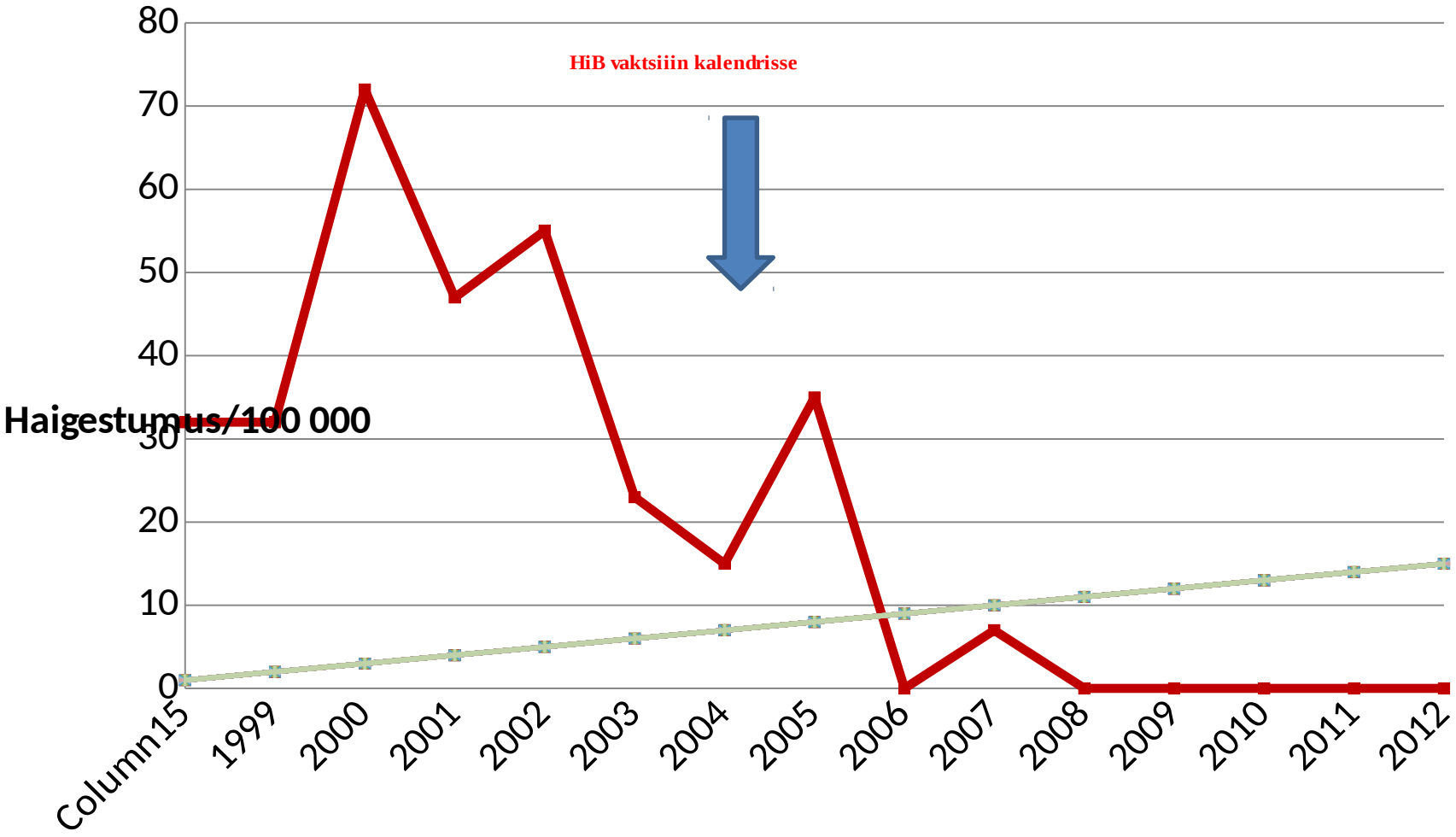
„Kolmanda põlvkonna” vaktsiinid

- **80ndad -**

Konjugeerimine - mikroobi kapsulaarse polüsahhariidi liitmine valgulise kandjaga (TT-teetanuse toksoid, DT-difteeria toksoid, DT CRM197) .

Kapsulaarsed polüsahhariidvaktsiinid (*H.influenzae* B, *N.meningitidis* A, C, Y, W135, *S.pneumoniae* erinevad serotüübid) – ei ole immunogeensed < 2 aasta vanustele lastele, puudub immuunmälu ja karjaefekt.

< 1 aasta vanuste laste haigestumus HiB meningiiti Eestis aastatel 1998-2012



Tamm E, Laan M, Zilmer K, Torm jt. BLK 2013

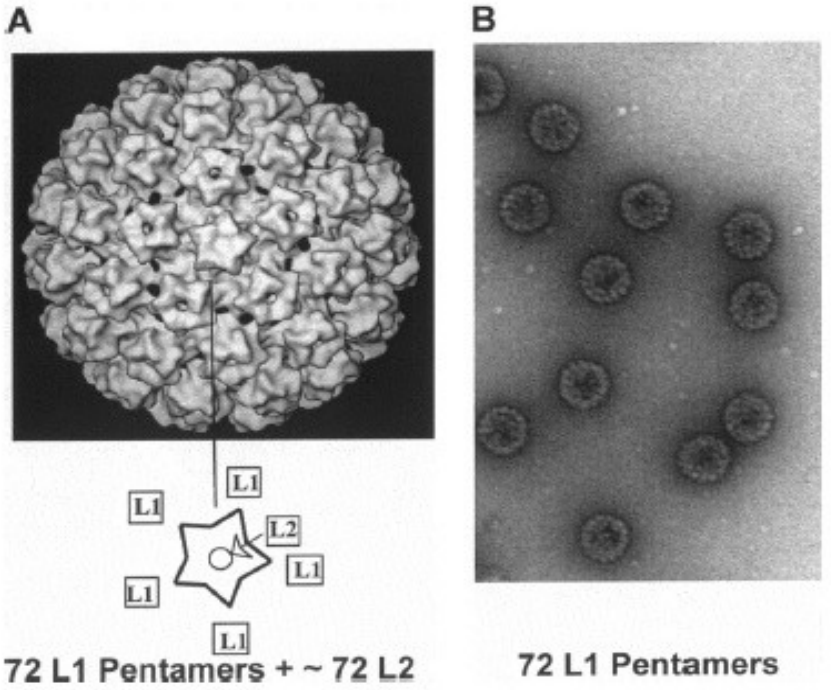
Geenitehnoloogia rakendamine - võimaldas bakterite, seente, loomsete ja insektide rakkudel muutuda immunogeensete valkude tootmise substraadiks.

Rekombinantsed vaktsiinid

B-hepatiidi vaktsiin

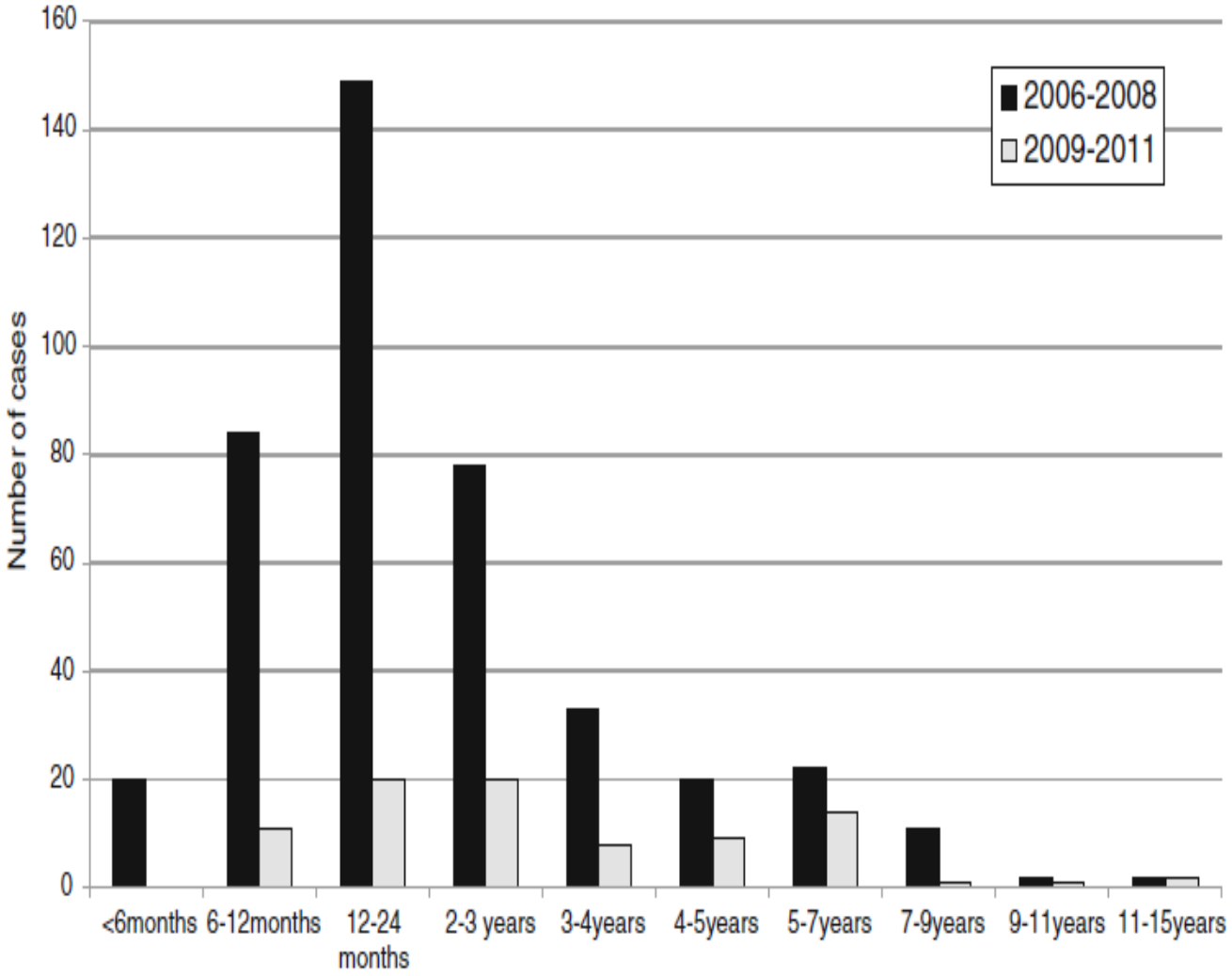
Papilloomi viiruse vaktsiin

Rotaviiruse vaktsiin



Tampere Ülikooli Haiglasse või EMO-sse pöördunud ägeda RVGE lapsed

Fig. 2 Reduction of RVGE between 2006–2008 and 2009–2011 in different age groups



Hemming, Räsanen et al. Eur J Pediatr 2013

Pöördvaktsinoloogia
(Reverse vaccinology)

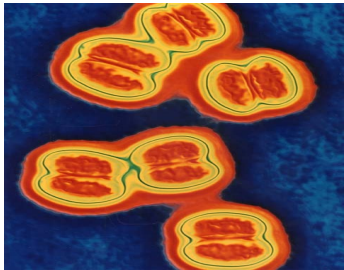
- 1995 esimene genoomi sekveneerimine: H.influenzae

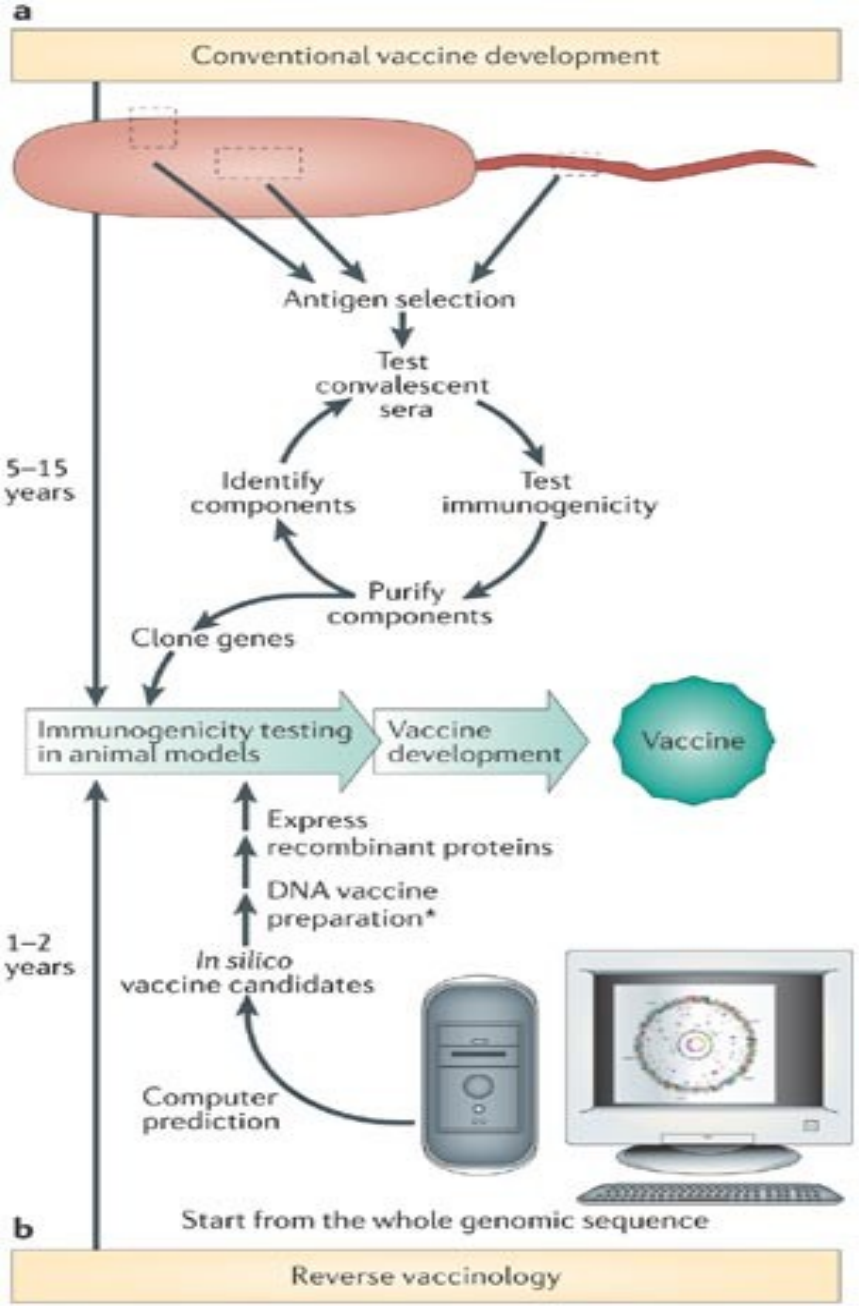
Võimaldas määrata mikroobide kogu antigeense repertuaari ja leida ja testida nende seast potentsiaalseid vaktsiinikandidaate.

Pöördvaktsinoloogia tehnoloogia – mikroobi genoomi poolt kodeeritud kõikide potentsiaalsete antigeenide identsifitseerimine ja testimine.

Ebaõnnestunud katsed luua B-grupi meningokoki vastane vaktsiin. Bioinformaatilise analüüsi abil leiti 2159 valgu seast üle 600 potentsiaalse antigeeni, millest 30 olid võimelised indutseerima antikehade tekke. 3 antigeeniga hakati arendama vaktsiini.

- Bexsero – litsenseeriti 2013.a.





Nature Reviews | Microbiology

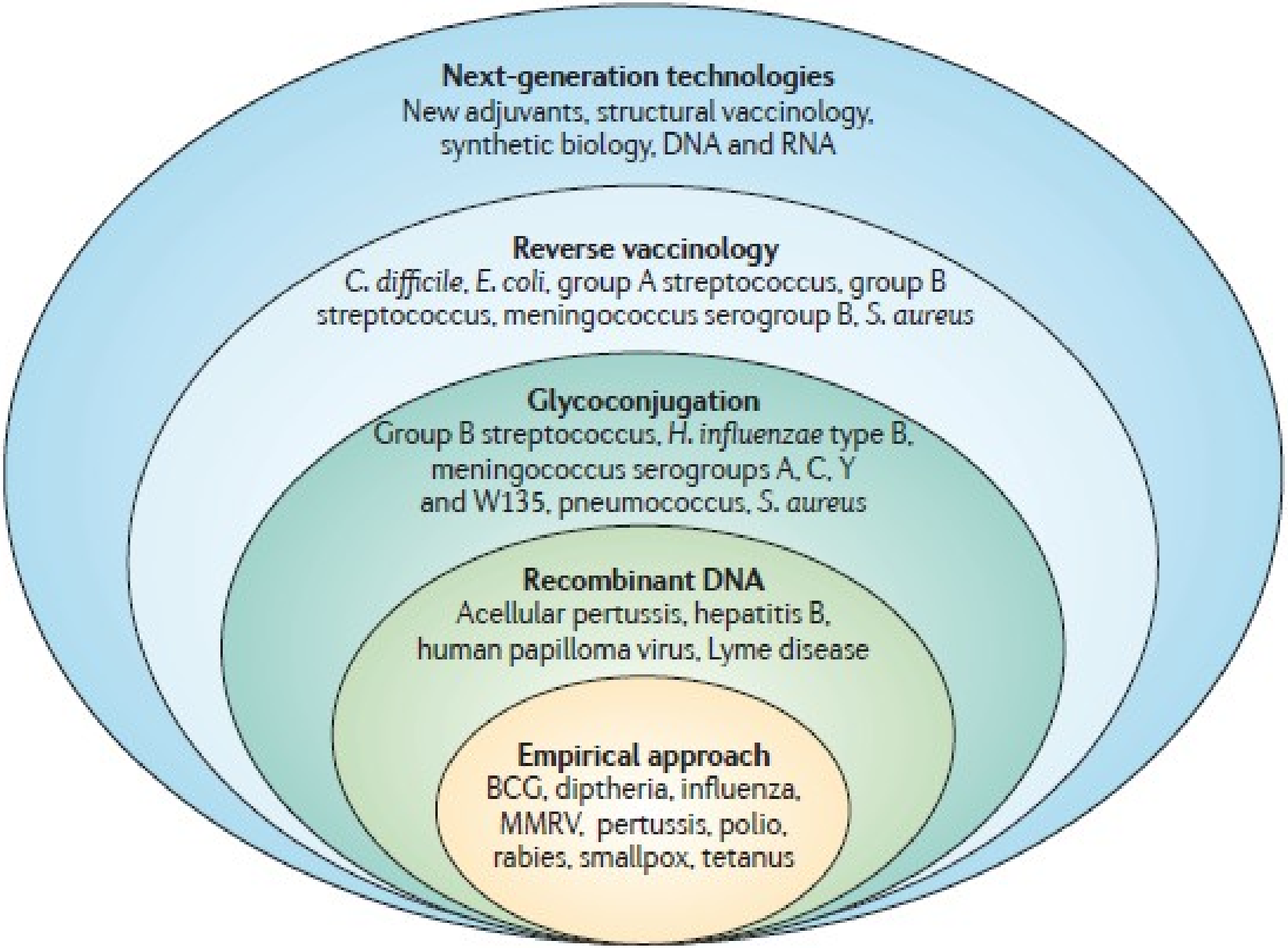
Adjuvandid

Table 1 | **Vaccine adjuvants**

Adjuvant name (year licensed)	Adjuvant class	Components	Vaccines (disease)
Adjuvants licensed for use in human vaccines			
Alum* (1924)	Mineral salts	Aluminium phosphate or aluminium hydroxide	Various
MF59 (Novartis; 1997)	Oil-in-water emulsion	Squalene, polysorbate 80 (Tween 80; ICI Americas), sorbitan trioleate (Span 85; Croda International)	Fluad (seasonal influenza), Focetria (pandemic influenza), Aflunov (pre-pandemic influenza)
AS03 (GlaxoSmithKline; 2009)	Oil-in-water emulsion	Squalene, Tween 80, α-tocopherol	Pandremix (pandemic influenza), Prepandrix (pre-pandemic influenza)
Virosomes (Berna Biotech; 2000)	Liposomes	Lipids, hemagglutinin	Inflexal (seasonal influenza), Epaxal (hepatitis A)
AS04* (GlaxoSmithKline; 2005)	Alum-absorbed TLR4 agonist	Aluminium hydroxide, MPL	Fendrix (hepatitis B), Cervarix (human papilloma virus)
Vaccine adjuvants tested in humans but not licensed for use			
CpG 7909, CpG 1018	TLR9 agonist	CpG oligonucleotides alone or combined with alum/emulsions	–
Imidazoquinolines	TLR7 and TLR8 agonists	Small molecules	–
Poly I:C	TLR3 agonist	Double-stranded RNA analogues	–
Pam3Cys	TLR2 agonist	Lipopeptide	–
Flagellin	TLR5 agonist	Bacterial protein linked to antigen	–
Iscomatrix	Combination	Saponin, cholesterol, dipalmitoylphosphatidylcholine	–
AS01	Combination	Liposome, MPL, saponin (QS21)	–
AS02	Combination	Oil-in-water emulsion, MPL, saponin (QS21)	–
AF03	Oil-in-water emulsion	Squalene, Montane 80, Eumulgin B1 PH	–
CAF01	Combination	Liposome, DDA, TDB	–
IC31	Combination	Oligonucleotide, cationic peptides	–

AF03, adjuvant formulation 03; CAF01, cationic adjuvant formulation 01; DDA, dimethyldioctadecylammonium; MPL, monophosphoryl lipid A; Pam3Cys, tripalmitoyl-S-glyceryl cysteine; Poly I:C, polyinosinic–polycytidylic acid; TDB, trehalose dibehenate; TLR, Toll-like receptor. *Adjuvants licensed in the United States.

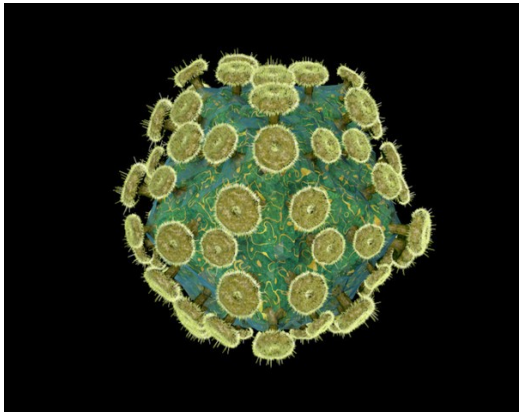
Rappuoli et al . Nature 2011

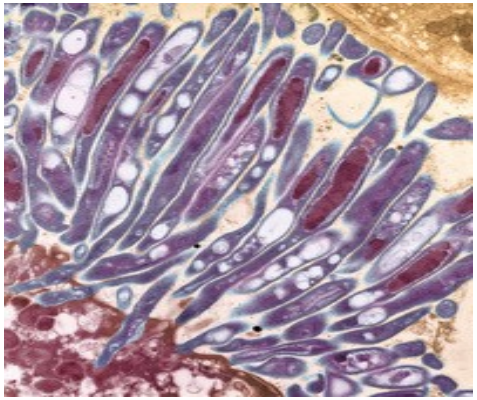


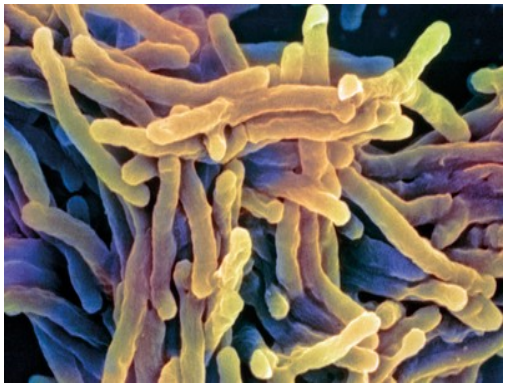
Finco, Rappuoli. Frontiers in Immunol. 2014

Big Five

Big Three

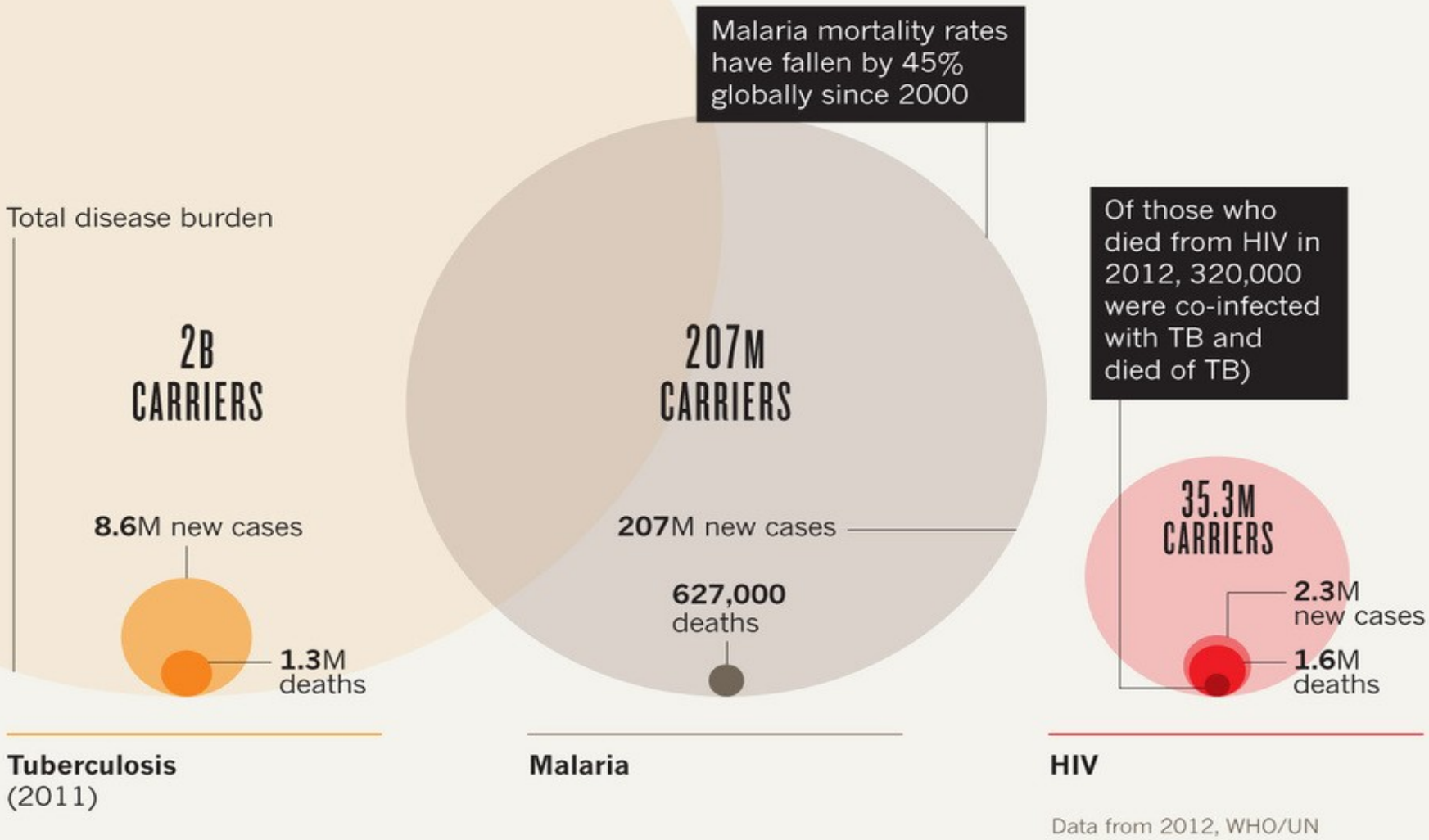






PATHOGENS ON THE RAMPAGE

Three of the deadliest diseases on Earth still lack effective vaccines.



Data from 2012, WHO/UN

Tuberkuloosi vaktsiin

12 potentsiaalset vaktsiini kliinilistes uuringutes

Ei ole siiani selge, milline üldse on tbc vastane

immuunsus

- Miks BCG kutsub esile kaitse?
- Miks immuunsus ei hoia ära latentset infektsiooni ?
- Missugust immuunvastust on vaja, et hoida ära latentse infektsiooni reaktiveerumine?

Table 1. Preventive tuberculosis vaccine candidates in clinical trials

Name	Construct	Type	Primary target population	Status
Protein-adjuvant				
H1	Antigen: Rv1886+Rv3875 fusionprotein; Adjuvant: IC31 or CAF01	Preexposure	Heterologous boost on top of BCG prime, for infants	Phase I completed (probably replaced by H56)
H4	Antigen: Rv1886+Rv0288 fusion protein; Adjuvant: IC31	Preexposure	Heterologous boost on top of BCG prime, for infants	Phase I completed
H56	Antigen: Rv1886+Rv3875 +Rv2660 fusion protein; Adjuvant: IC31	Preexposure/ postexposure (multistage)	Heterologous boost on top of BCG prime, for adolescents and adults	Phase I completed
M72	Antigen: Rv1196+Rv0125 fusion protein; Adjuvant: AS01	Preexposure/ postexposure (multistage)	Heterologous boost on top of BCG prime, for adolescents and adults	Phase IIa completed
ID93	Antigen: Rv2608+Rv3619 +Rv3620+Rv1813 fusion protein; Adjuvant: GLA-SE	Preexposure/ postexposure (multistage)	Heterologous boost on top of BCG prime, for adolescents and adults	Phase I
Viral-vectored				
MVA85A	Antigen: Rv3804; Carrier: MVA	Preexposure	Heterologous boost on top of BCG prime, for infants	Phase IIb completed (no efficacy)
MVA85A	Antigen: Rv3804; Carrier: MVA	Preexposure	Heterologous boost on top of BCG prime, for adolescents and adults	Phase IIb
Crucell Ad35 /Aeras 402	Antigen: Rv3804 +Rv1886+Rv0288; Carrier: human Ad35	Postexposure	Heterologous boost on top of BCG prime, for adolescents and adults	Redirected to phase IIa
Crucell Ad5-MVA85A	Antigen: Rv3804 +Rv1886+Rv0288 (Ad35) Rv3804 (MVA); Carriers: Ad35 and MVA	Postexposure	Heterologous boost–boost on top of BCG prime, for adolescents and adults	Phase I
FP85A±MVA85A	Antigen: Rv3804; Carriers: FP±MVA	Postexposure	Heterologous boost–boost on top of BCG prime	Phase I completed (no immunogenicity)
Ad5HUAg85A	Antigen: Rv3804; Carrier: human Ad5	Postexposure	Heterologous boost on top of BCG prime, for adolescents and adults	Phase I completed
Viable vaccines				
VPM1002	rBCGΔureC::hly (viable rBCG)	Preexposure	Prime, as BCG replacement, for infants	Phase IIa
MTBVAC	rMtbΔPhoPΔFadD26 (viable rMtb deletion mutant)	Preexposure	Prime, as BCG replacement, for infants	Phase I

Kaufmann S.

Curr Opinion in Pulmon. Med. 2014

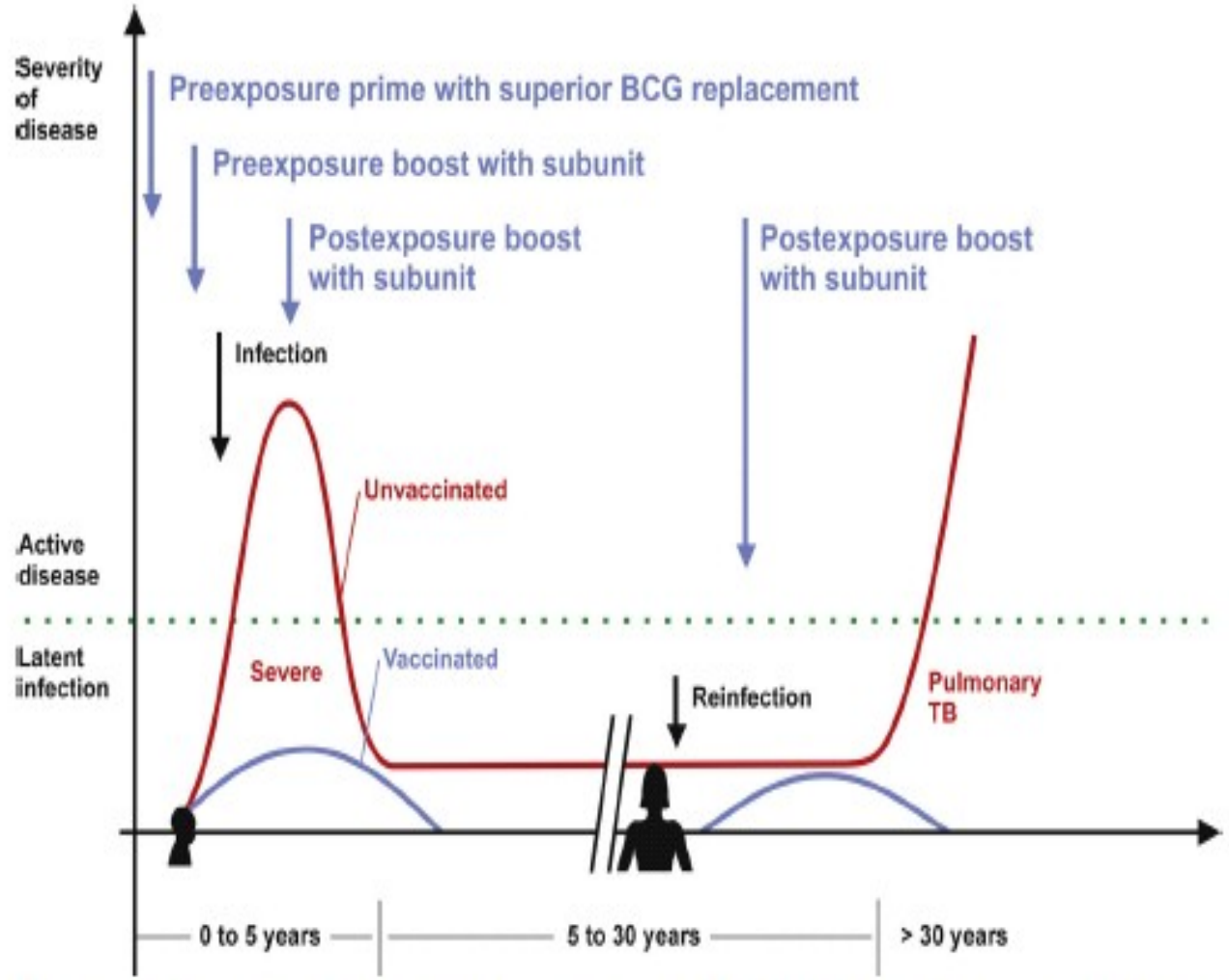


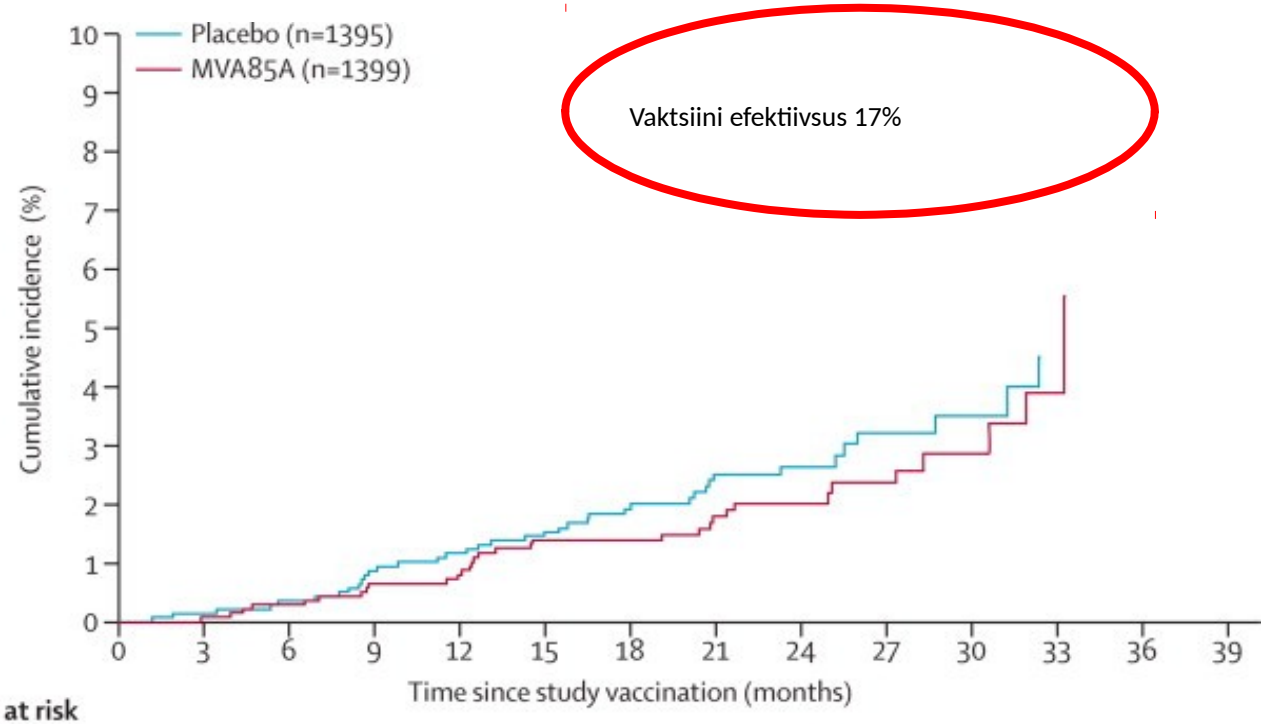
Fig. 3. Optimal prime-boost vaccination regime against TB. Note that booster vaccines could either be identical, since they comprise both active antigens and dormancy antigens, or different, for preexposure versus postexposure, with preexposure vaccines comprising active antigens and postexposure vaccines comprising dormancy antigens. Abbreviations: BCG, bacille Calmette–Guérin; TB, tuberculosis.

Kaufmann S. Seminars in Immunology 2013

Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

Michele D Tameris*, Mark Hatherill*, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, J Bruce McClain, Gregory D Hussey, Willem A Hanekom, Hassan Mahomed†, Helen McShane†, and the MVA85A 020 Trial Study Team

Lancet 2013; 381: 1021–28

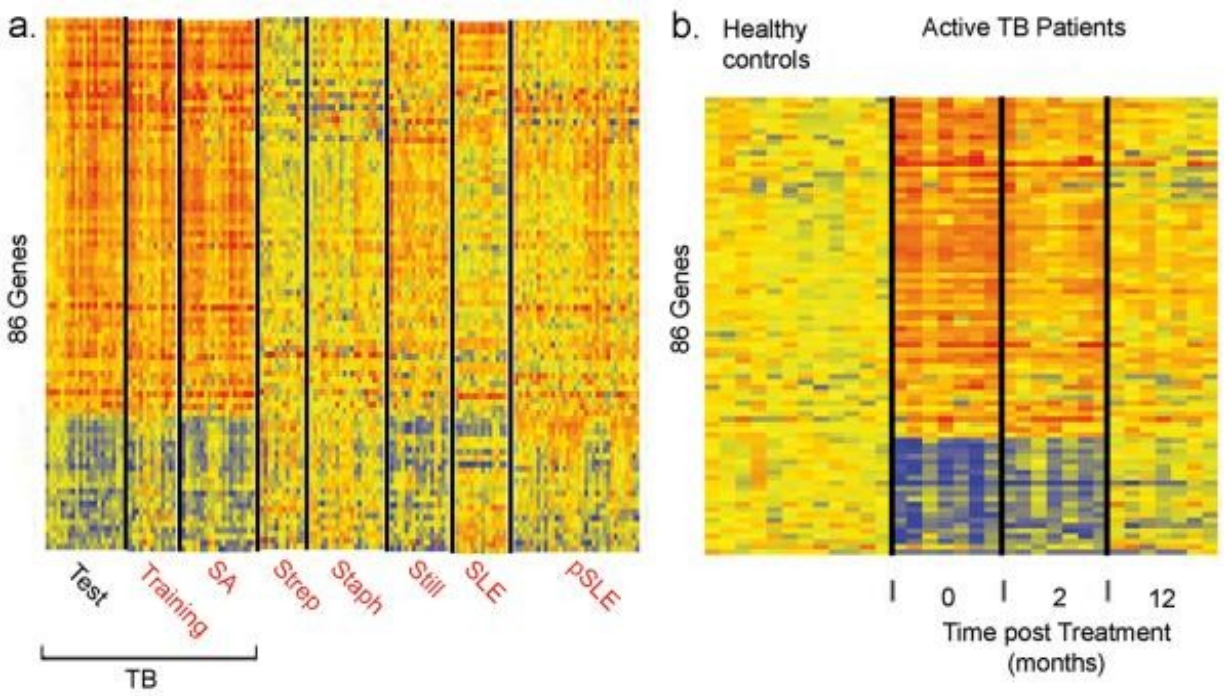


Number at risk

Placebo	1395	1380	1375	1364	1349	1334	1180	956	741	500	340	103	25	0
MVA85A	1399	1385	1378	1361	1343	1328	1182	944	731	500	331	98	16	0

Süsteemibioloogia rakendamine

Kasutatakse bioinformaatikat, et läbi sõeluda suur hulk geeni-uuringutega saadud andmeid, et leida biomarkereid.



<u>Rahvusvaheline multitsentriline biomarkereid tuvastav uuring</u>

850 patsienti – LAV-st, Etiooopiast ja Gambiast – TBC diagnoosimese hetkel.

4500 kontaktset nende lähikonnast.

Iga 6 kuu järel uuritakse nende inimeste geenide ekspressiooni ja metabolismi.

Vrd neid, kellel kujuneb ja kellel mitte tbc (Max Plancki Instituut Berliinis ja Seattle Biomeditsiini Teadusinstituut Washingtonis)

Eesmärgiks leida biomarkereid, mis seostuvad suurema haigusriskiga.

Bourzac K, Nature 2014

Year Completed	Product/ Clade/ Trial Name	Countries	Number Of Participants	Result
2003	AIDSVAX B/B VAX003	Canada, Netherlands, Puerto Rico, US	5,417	No effect
2003	AIDSVAX B/E VAX004	Thailand	2,546	No effect
2007	MRK-Ad5 B Step	Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico, US	3,000	Immunizations halted early for futility; subsequent data analysis found potential for increased risk of HIV infection among Ad5-seropositive, uncircumcised men.
2007	MRK-Ad5 B Phambili	South Africa	801	Immunizations halted based on Step result; additional data presented in May 2013.
2009	ALVAC-HIV (vCP1521) and AIDSVAX B/E Thai Prime-Boost/RV 144	Thailand	16,402	Modest effect (31.2%)
2013	DNA and Ad5 A/B/C HVTN 505	US	2,500	Immunizations halted early for futility; vaccine regimen did not prevent HIV infection nor reduce viral load among vaccine recipients who became infected with HIV; follow-up continues.

LETTER

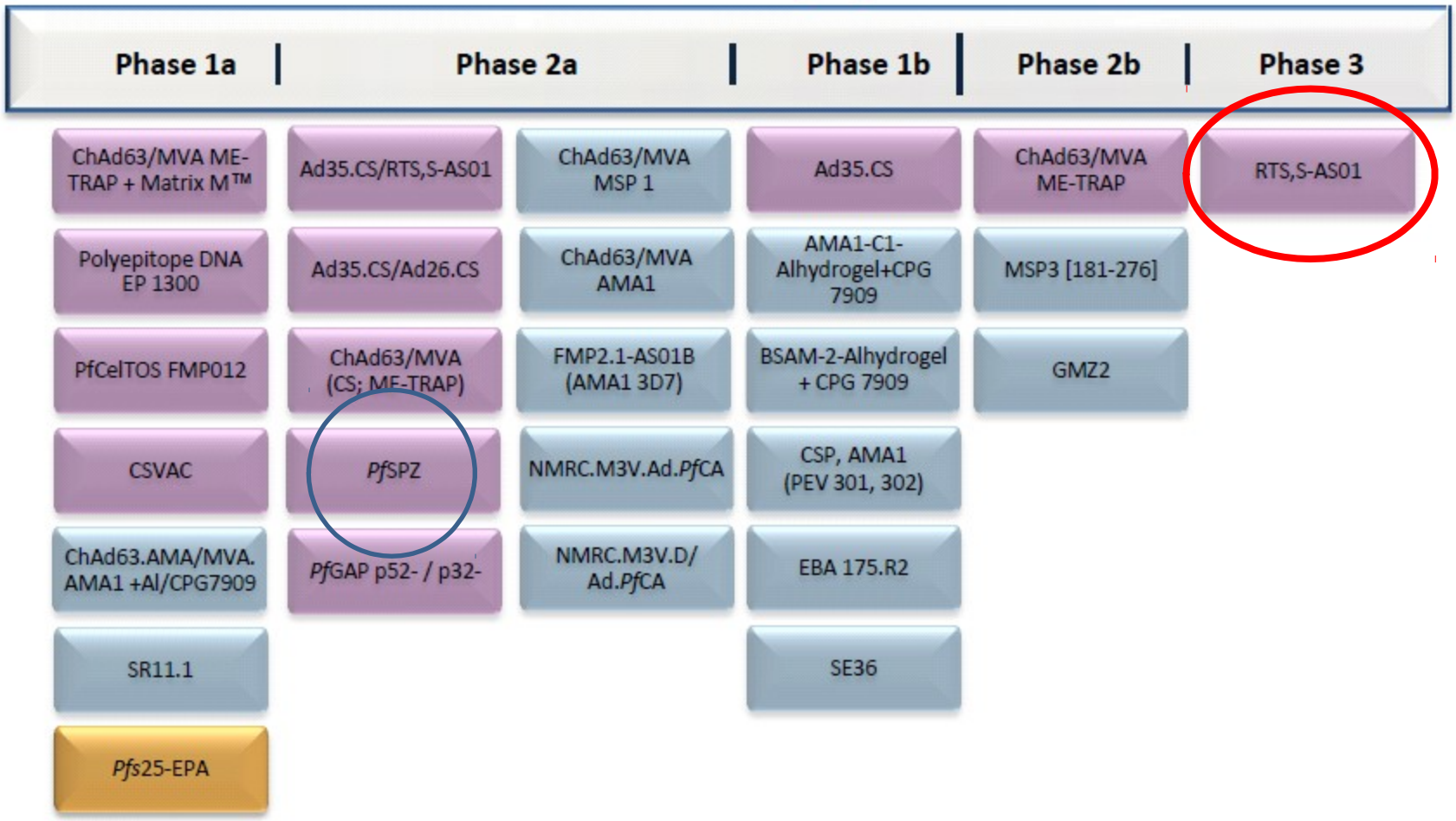
doi:10.1038/nature12519

Immune clearance of highly pathogenic SIV infection

Scott G. Hansen[1]*, Michael Piatak Jr[2]*, Abigail B. Ventura[1], Colette M. Hughes[1], Roxanne M. Gilbride[1], Julia C. Ford[1], Kelli Oswald[2], Rebecca Shoemaker[2], Yuan Li[2], Matthew S. Lewis[1], Awbrey N. Gilliam[1], Guangwu Xu[1], Nathan Whizin[1], Benjamin J. Burwitz[1], Shannon L. Planer[1], John M. Turner[1], Alfred W. Legasse[1], Michael K. Axthelm[1], Jay A. Nelson[1], Klaus Früh[1], Jonah B. Sacha[1], Jacob D. Estes[2], Brandon F. Keele[2], Paul T. Edlefsen[3], Jeffrey D. Lifson[2] & Louis J. Picker[1]

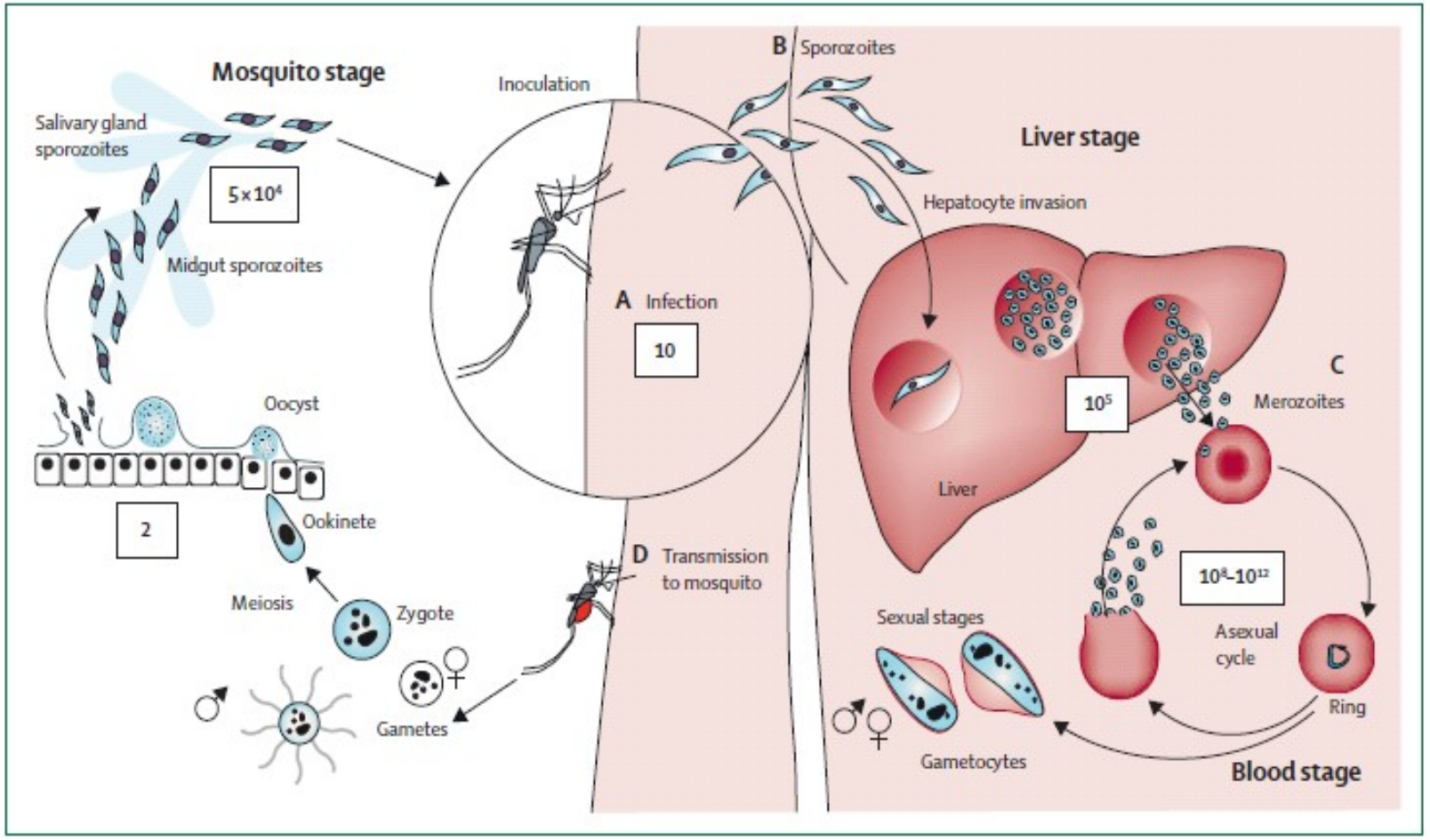
- SIV ag ekspresseeritud CMV vektoril
- Vaktsineeriti kroonilise infektsiooniga ahve
- Tekkisid nii ak kui ka aktiveeriti T-lümfotsüütide mälurakud.
- Ahvid muutusid viirusevabaks
- Loodetakse, et vaktsiini efekt on pikaajaline
- Välja töötamisel sama vaktsiin HIV viiruse vastu

Global malaria vaccine pipeline



***P. falciparum* vaccines:** Pre-erythrocytic Blood-stage Transmission-blocking
***P. vivax* vaccines:** Pre-erythrocytic Blood-stage Transmission-blocking

Data source: http://www.who.int/vaccine_research/links/Rainbow/en/index.html



White NJ et al. Lancet 2014

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 17, 2011 VOL. 365 NO. 20

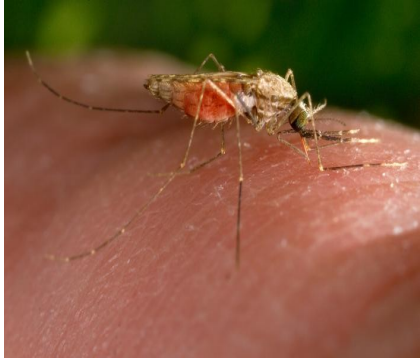
First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children

The RTS,S Clinical Trials Partnership*

- Uuringus 15 000 last, 11 keskusest sub-Sahaara Aafrika regioonist
- 18 kuud järelkontrollil 47% vähem haigusjuhte

5-17k vanustel lastel

- 27% vähem 6-12n vrd mittevaktsineeritutega



S.Hoffman (Sanaria) -

Kasvatas moskiitosid, toites neid parasiitidega nakatunud verega. Sporozoidid süljenäärmetes, kiiritatakse ja puhastatakse. Vaktsiin i/m süstena ei töötanud

Kliiniline uuring 40 täiskasvanul

(Seder, Chang, Enama et al Science 2013)

- 6 doosi iv süstena
- Hea efektiivusega
- Suurem uuring Tansaanias ja Malis

Inaktiveeritud vaktsiinid

Jansen et al 2008 [28]	2003–05	18–72 months	PCR-confirmed influenza	51% (IIV + PCV) 52% (IIV alone)	Study of IIV + PCV, IIV alone, or placebo. Also looked at reduction in febrile respiratory illness.
Vesikari et al 2011 [51]	2007–08 2008–09	6–72 months	PCR-confirmed influenza	43% (overall) 45% (strain-matched)	H3N2-predominant. Study also had adjuvanted IIV arm.
Loeb et al 2010 [88]	2008–09	36 months–15 years	PCR-confirmed influenza	59%	Cluster randomized. Study population of Hutterite communities.

Adjuvandiga vaktsiinid

Esposito et al 2003 [89]	2000–01	6 months–9 years	URIs, hospitalizations, and school absenteeism	27% (URIs) 60% (hospitalizations) 61% (school absenteeism)	Virosomal-adjuvanted intranasal IIV. H1N1-predominant season. Also VE of 39% in reducing medical visits among household contacts.
Principi et al 2003 [101]	2001–02	6 months–5 years	URIs, hospitalizations, and school absenteeism	33% (URIs) 50% (hospitalizations) 48% (school absenteeism)	Virosomal-adjuvanted intramuscular IIV. Indirect effects also reported.
Vesikari et al 2011 [51]	2007–08 2008–09	6–72 months	PCR-confirmed influenza	86%	H3N2-pred. Study also had unadjuvanted IIV arm.

Elus, nõrgestatud viiruseid sisaldavad vaktsiinid

Tam et al 2007 [102]	2000–03	12–36 months	Culture-confirmed influenza	70% (Year 1) 64% (Year 2)	Protection against strain-matched infections: 73% (Year 1), 84% (Year 2).
Vesikari et al 2006 [74]	2000–02	6–36 months	Culture-confirmed influenza	85% (Year 1) 89% (Year 2)	Highest VE for both years against H1N1 and H3N2 (slightly lower for B).
Bracco Neto et al 2009 [103]	2001–03	6–36 months	Culture-confirmed influenza	74% (Year 1) 74% (Year 2)	VE for single dose was 58% (Year 1) and 65% (Year 2) in this age group.

Lafond K et al J of Ped Inf.Dis 2013

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oil-in-Water Emulsion Adjuvant with Influenza Vaccine in Young Children

Timo Vesikari, M.D., Markus Knuf, M.D., Peter Wutzler, M.D.,

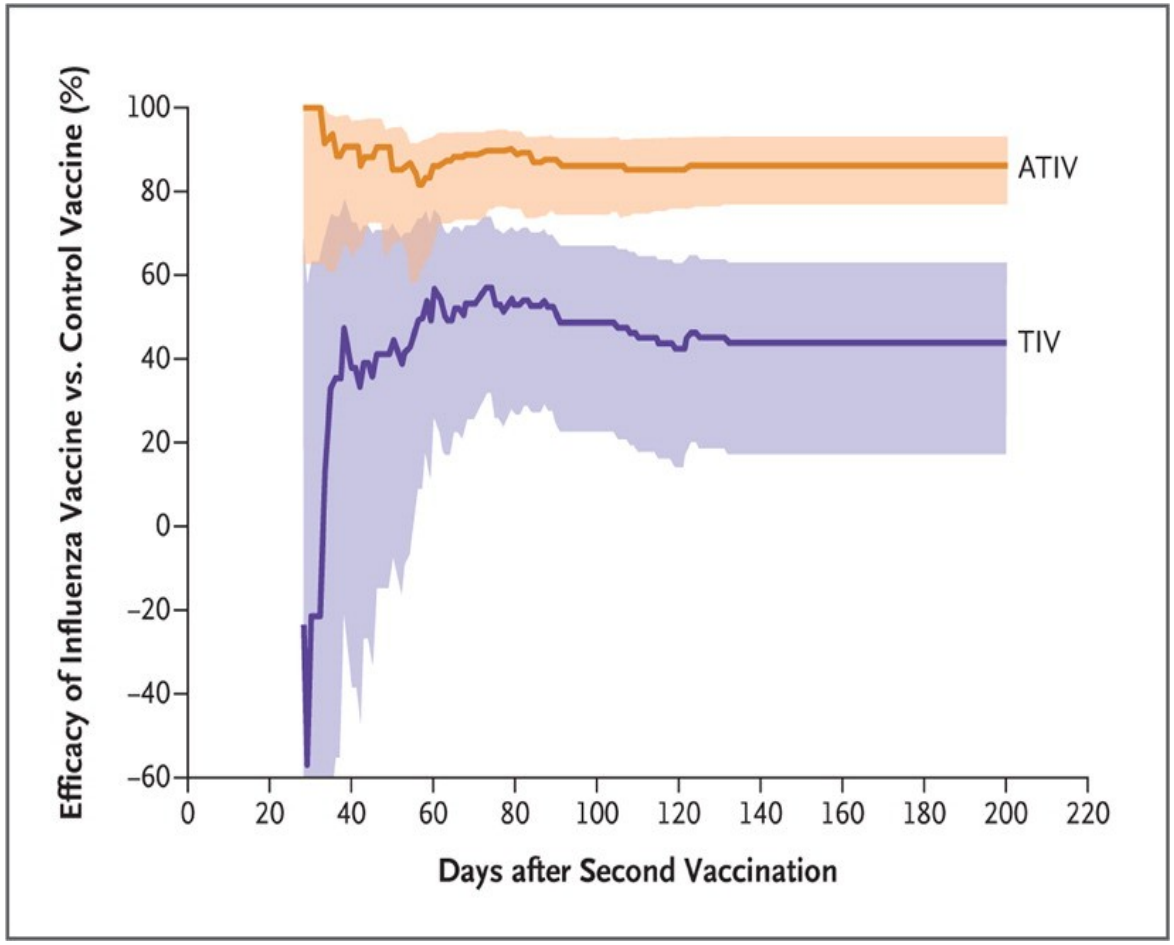


Figure 2. Efficacy of Influenza Vaccines versus Control Vaccine over Time.

The cumulative efficacy of ATIV and of TIV, as compared with control (noninfluenza) vaccine, is shown. The data are for efficacy against all viral strains over time after the second dose of vaccine in children 6 to less than 72 months of age. Shaded areas represent 95% confidence intervals.

Gripi vaktsiinid lähitulevikus:

- Traditsioonilised inaktiveeritud vaktsiinid:

  Viiruste kasvatamine rakukultuuril

  Antigeeni doosi suurendamine

  Adjuvandi lisamine

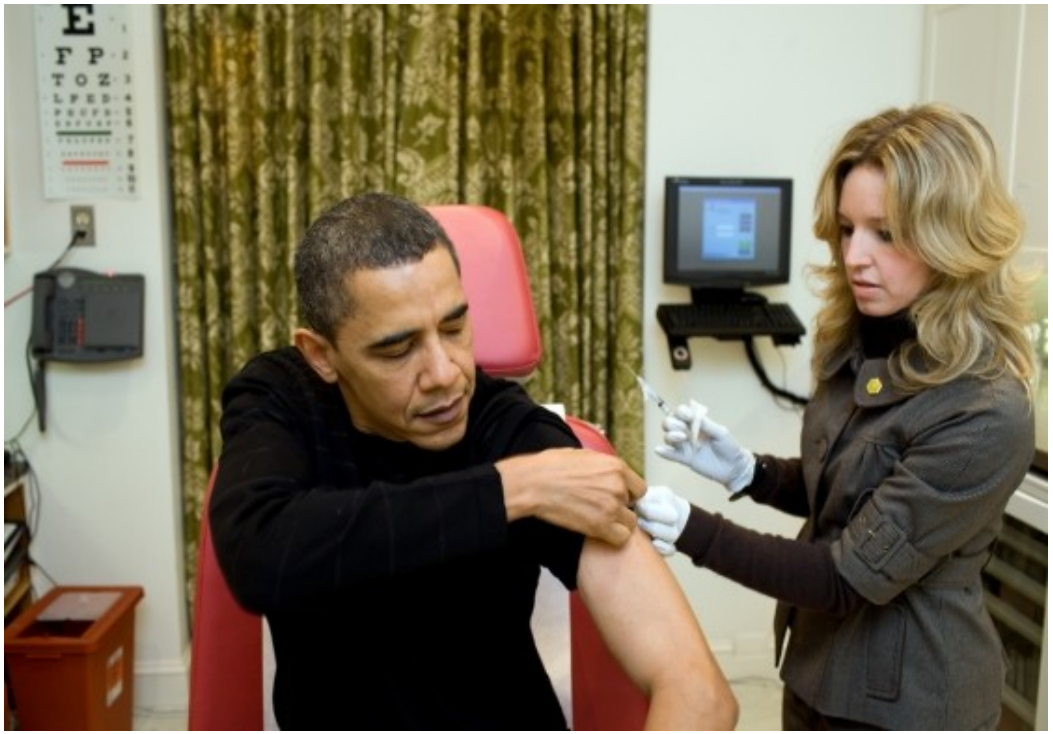
  Intradermaalselt vaktsiini manustamine

  4-valentne vaktsiin (2A- ja 2B-tüve)

- Universaalne gripivastane vaktsiin

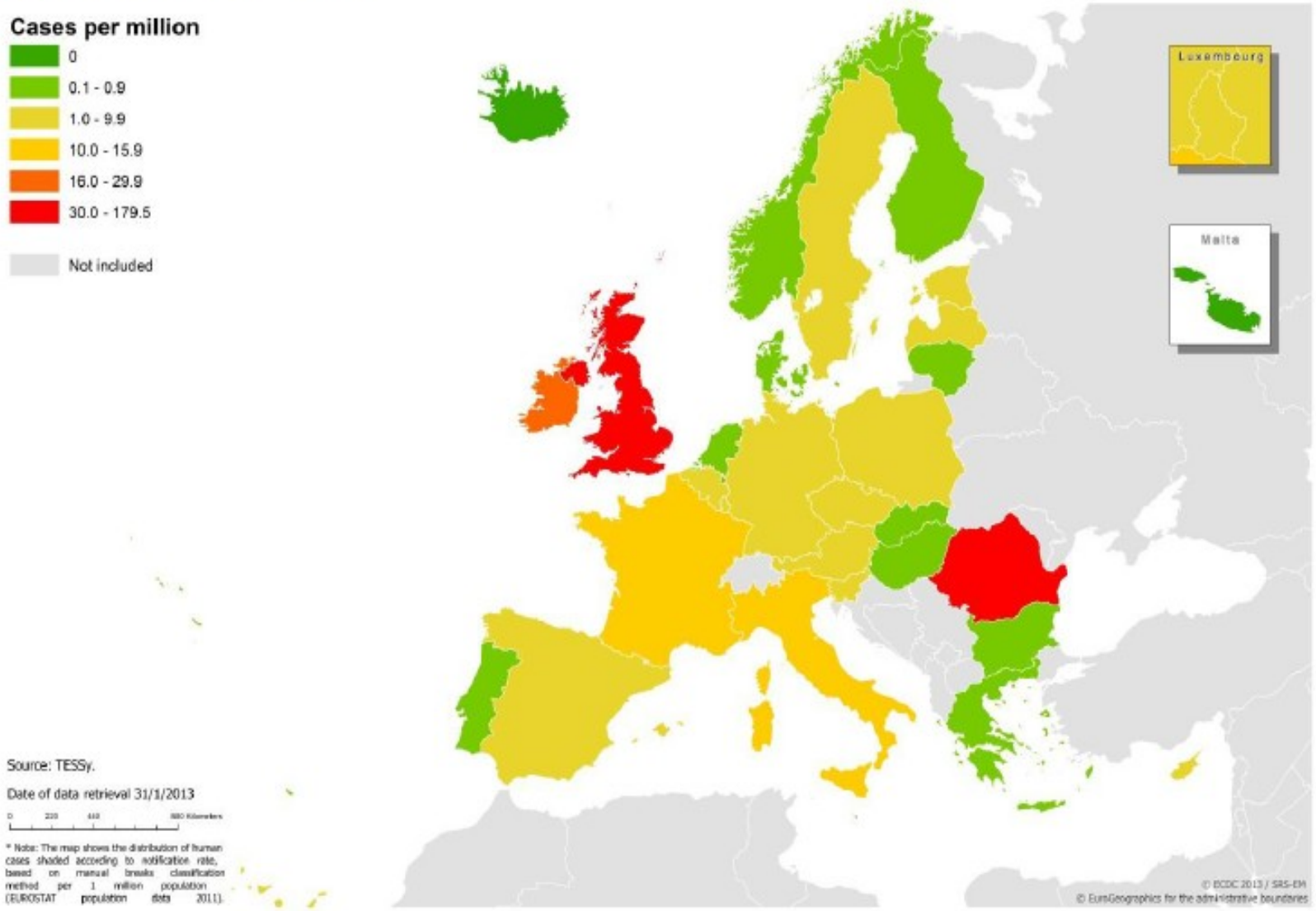
Table 1. Viral targets of universal vaccines

Protein	Targeted site	Function of target	Proposed mechanism(s) of protection
Hemagglutinin (HA)	Stem	Fusion activity	Inhibition of fusion, maturation of the HA, viral egress, and ADCC
Matrix 2 (M2)	Ectodomain of M2 (M2e)	Ion channel	Alveolar macrophages and Fc ADCC Antibody-dependent NK cell activity Complement-mediated lysis
Nucleoprotein (NP)	T cell and antibody epitopes	T cell stimulation and non-neutralizing antibody	Cell lysis by $CD8^+$ cytotoxic T lymphocytes (CTL) $CD4^+$ T lymphocyte-mediated cytolysis and B cell stimulation
Matrix 1 (M1)	T cell epitopes	T cell stimulation	Cell lysis by $CD8^+$ cytotoxic T lymphocytes (CTL) $CD4^+$ T lymphocyte-mediated cytolysis and B cell stimulation
Neuraminidase (NA)	Conserved sialidase active site	Sialidase	Inhibition of viral spread

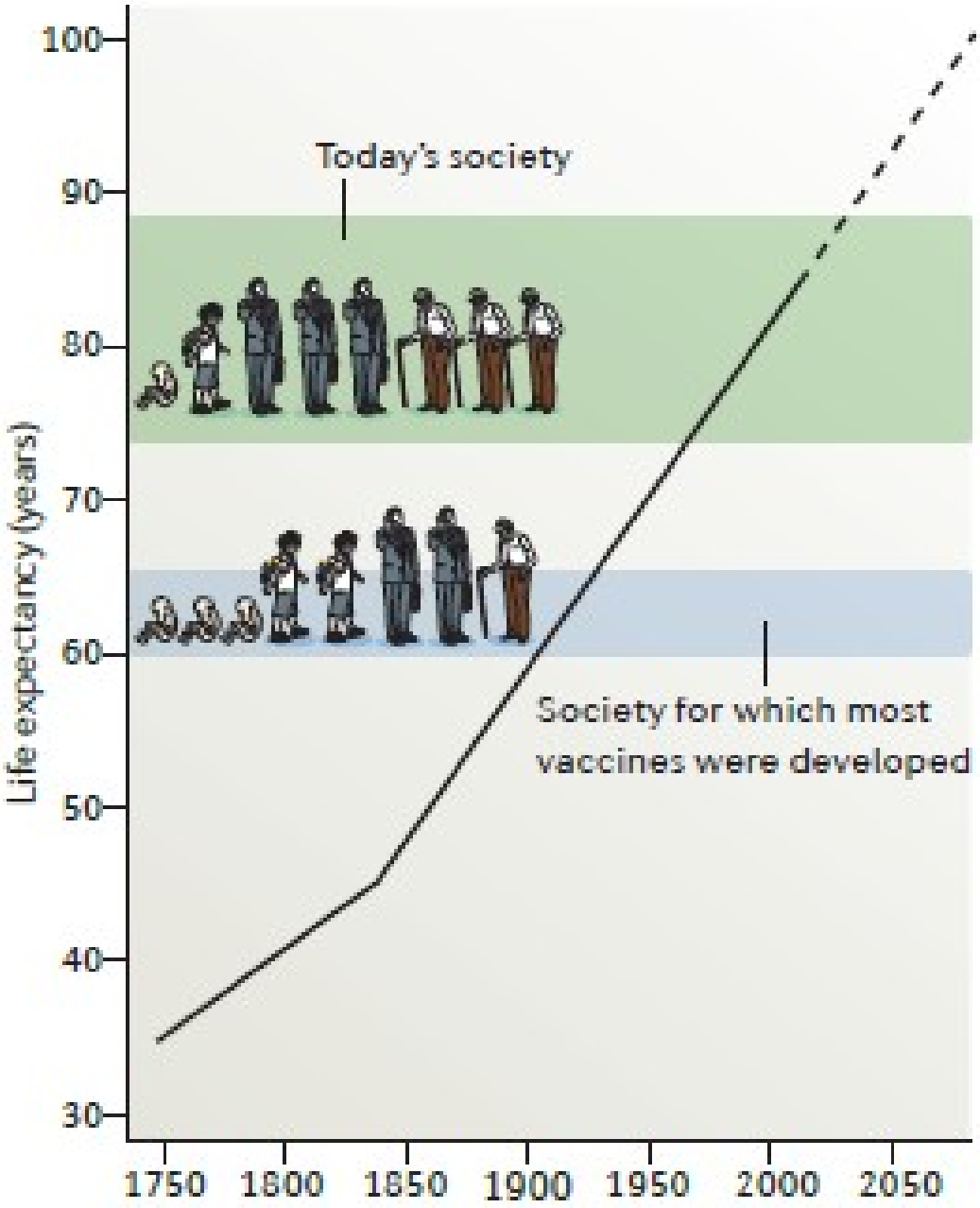


?

Figure 5. Measles notification rates (cases per million) by country, January – December 2012, EU/EEA countries (n=8 230)



Vanemate poolt laste vaktsineerimata jätmine peaks olema ühiskonna poolt mitteaktsepteeritav



Adults

- Diphtheria
- Hepatitis B virus
- Influenza virus
- Meningococcus serogroups A, B, C, Y and W135
- Pertussis
- Respiratory syncytial virus
- Tetanus

Elderly

Recurrent infections:

- Group B streptococc
- Influenza virus
- Meningococcus sero A, B, C, Y and W135
- Pneumococcus
- Respiratory syncytia
- Varicella zoster virus

Antibiotic resistance:

- *Acinetobacter baumannii*
- *C. difficile*
- *Candida* spp.
- Enterotoxigenic *E. coli*
- *Klebsiella pneumoniae*
- *P. aeruginosa*
- *S. aureus*

Cancer:

- Breast cancer
- Colorectal cancer
- Prostate cancer

Rappuoli et al Nat Rev.2012

Meedia ja kommunikatsioon

- ,,*Peres on küll lastele põhivaktsiinid ära tehtud, kuid eelkõige seepärast, et ei* ***tekiks hiljem probleeme lennukisse pääsemisega või lasteaeda saamisega”***

- ,,*Minu põhimõte on see, et* ***ma ei torgiks loodust****.”*

Ajakiri Naised, elu24.ee

- Liis Tappo-Treial peab õigeks, et **vaktsineeritakse mõistlikkuse piires**.

  ,,Ma ei ole ka selle poolt, et nüüd keegi ei peaks vaktsineerima – kes teab, milline see tulemus lõpuks oleks," lisab ta.

- Näiteks ei ole pereema vaktsineerinud oma lapsi **punetiste, leetrite, mumpsi** ja teiste haiguste vastu, mille vaktsiinid on hiljem lisatud baasvaktsineerimise juurde."

- *,,**Mida vähem vaktsineerida, seda parem**. Kõik need suured üleskutsed gripivastaseks vaktsineerimiseks – ei tasu sattuda paanikasse igast kampaaniast, põed selle läbi ja ongi."*

Ajakiri Naised, elu24.ee

Kokkuvõtteks

,,Vaatamata poliitilise maailma ebakindlusele sisendavad uued tehnoloogiad optimismi, et vaktsineerimise kuldsele sajandile võib järgneda plaatina karva sajand.”

Stanley Plotkin ja Susan Plotkin