



Surto Ebola: O que sabemos até agora? O que dizer sobre tratamento e vacinas?

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Casos de Doença do Vírus Ebola 1976 - 2014



Year	Location	Virus	Species
1976	Democratic Republic of Congo	ZEBOV	Humans
1976	Sudan	SEBOV	Humans
1977	Democratic Republic of Congo	ZEBOV	Humans
1979	Sudan	SEBOV	Humans
1989-1990	USA	REBOV	Cynomolgus macaques
1992	Italy	REBOV	Cynomolgus macaques
1994	Gabon	ZEBOV	Humans
1994	Ivory Coast	CIEBOV	Chimpanzees, humans
1995	Democratic Republic of Congo	ZEBOV	Humans
1996	Gabon	ZEBOV	Humans
1996	Gabon	ZEBOV	Humans
1996	USA	REBOV	Cynomolgus macaques
2000-2001	Uganda	SEBOV	Humans
2001-2002*	Gabon	ZEBOV	Humans, gorillas, duikers
2001-2005*	Republic of Congo	ZEBOV	Humans, gorillas, chimpanzees, duikers
2004	Sudan	SEBOV	Humans
2007-2008*	Republic of Congo	ZEBOV	Humans
2007-2008	Uganda	BEBOV	Humans
2008	Philippines	REBOV	Swine

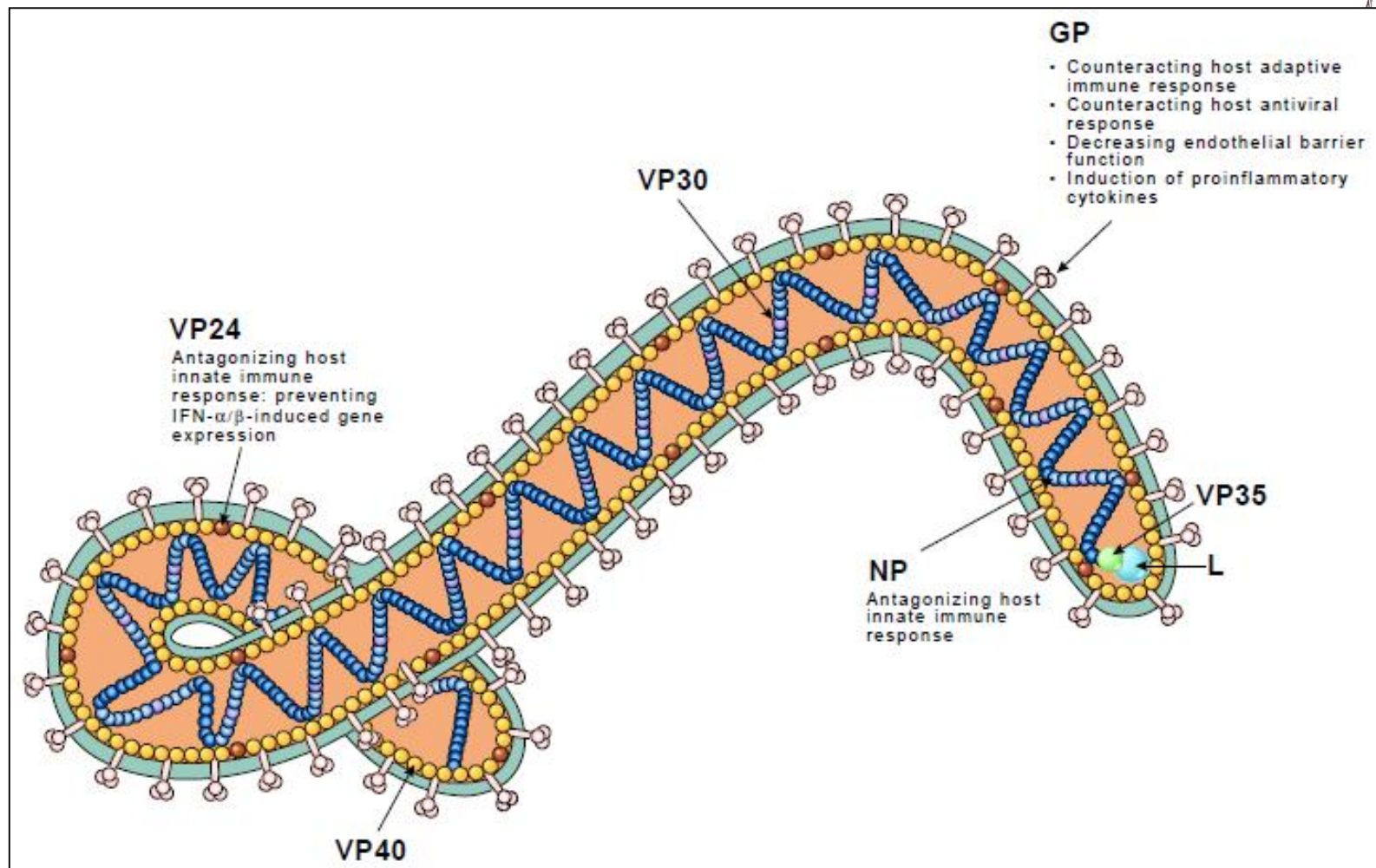
*Multiple independent outbreaks. Abbreviations: BEBOV, *Bundibugyo ebolavirus*; CIEBOV, *Côte d'Ivoire ebolavirus*; REBOV, *Reston ebolavirus*; SEBOV, *Sudan ebolavirus*; ZEBOV, *Zaire ebolavirus*.



Country	Town	Cases	Deaths	Species	Year
Multiple countries	multiple	4655*	2431*	<i>Zaire ebolavirus</i>	2014
Uganda	Luwero District	6*	3*	<i>Sudan ebolavirus</i>	2012
Dem. Rep. of Congo	Isiro Health Zone	36*	13*	<i>Bundibugyo ebolavirus</i>	2012
Uganda	Kibaale District	11*	4*	<i>Sudan ebolavirus</i>	2012
Uganda	Luwero District	1	1	<i>Sudan ebolavirus</i>	2011
Dem. Rep. of Congo	Luebo	32	15	<i>Zaire ebolavirus</i>	2008
Uganda	Bundibugyo	149	37	<i>Bundibugyo ebolavirus</i>	2007
Dem. Rep. of Congo	Luebo	264	187	<i>Zaire ebolavirus</i>	2007
South Sudan	Yambio	17	7	<i>Zaire ebolavirus</i>	2004
Republic of Congo	Mbomo	35	29	<i>Zaire ebolavirus</i>	2003
Republic of Congo	Mbomo	143	128	<i>Zaire ebolavirus</i>	2002
Republic of Congo	Not specified	57	43	<i>Zaire ebolavirus</i>	2001
Gabon	Libreville	65	53	<i>Zaire ebolavirus</i>	2001
Uganda	Gulu	425	224	<i>Zaire ebolavirus</i>	2000
South Africa	Johannesburg	2	1	<i>Zaire ebolavirus</i>	1996



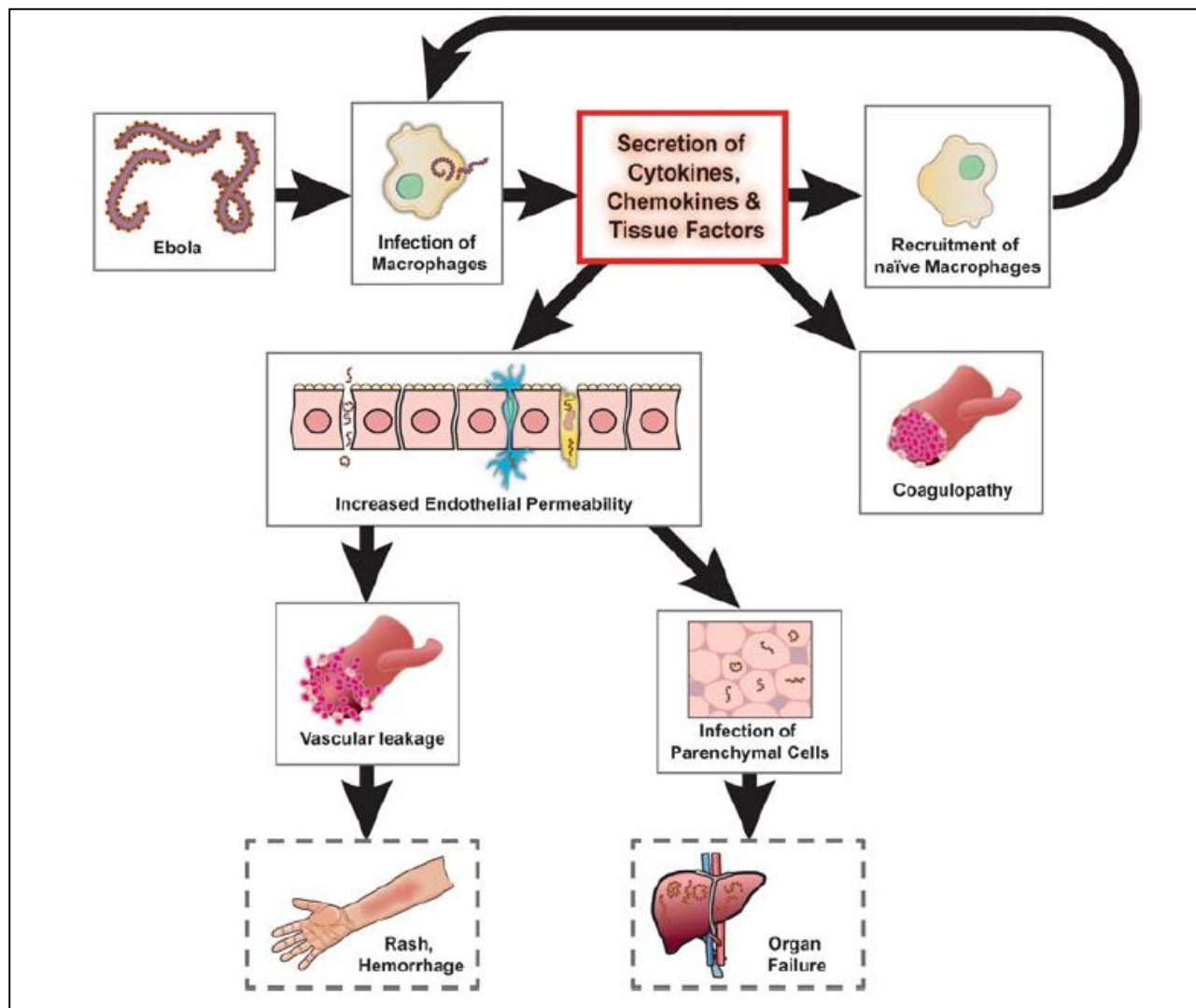
Determinantes de Patogenicidade



de Wit et al. *Genome Medicine* 2011, 3:5 (<http://genomemedicine.com/content/3/1/5>)



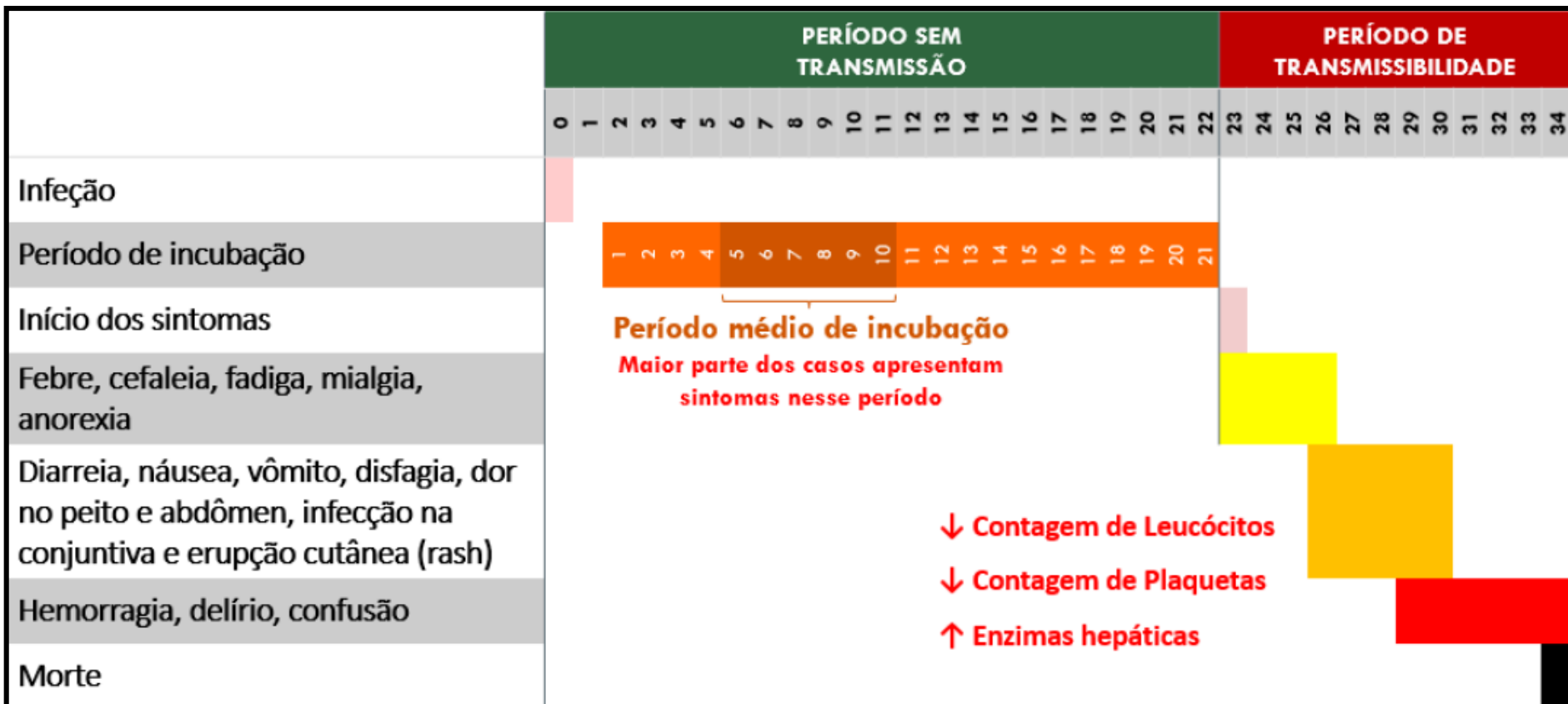
Resposta Imune



BioDrugs (2013) 27:565–583



História Natural da Doença



Fonte: MS



História Natural da Doença



Clinical Features of Ebola Virus Disease.

Phase of Illness	Time since Symptom Onset	Clinical Features
Early febrile	0–3 days	Fever, malaise, fatigue, body aches
Gastrointestinal	3–10 days	Primary: epigastric pain, nausea, vomiting, diarrhea Associated: persistent fever, asthenia, headache, conjunctival injection, chest pain, abdominal pain, arthralgias, myalgias, hiccups, delirium
Shock or recovery	7–12 days	Shock: diminished consciousness or coma, rapid thready pulse, oliguria, anuria, tachypnea Recovery: resolution of gastrointestinal symptoms, increased oral intake, increased energy
Late complications	≥10 days	Gastrointestinal hemorrhage, secondary infections, meningoencephalitis, persistent neurocognitive abnormalities*

* Secondary infections are presumptive diagnoses based on clinical features of distributive shock, oral or esophageal candidiasis, and oral ulcers; meningoencephalitis is a presumptive diagnosis based on clinical features of unconsciousness and stiff neck.

November 5, 2014 | D.S. Chertow and Others
(DOI: 10.1056/NEJMp1413084)



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Table 1. Characteristics, Symptoms, Vital Signs, and Time Course of Clinical Progression of 37 Patients with Confirmed Ebola Virus Disease (EVD).*

Variable	Value
Median age (IQR) — yr	38 (28–46)
Male sex — no. (%)	24 (65)
Health care worker — no. (%)	
Yes	14 (38)
No	23 (62)
Known mechanism of contact — no./total no. (%)†	
Health care	12/34 (35)
Household	23/37 (62)
Funeral	6/37 (16)
Known coexisting medical condition — no. (%)	
Hypertension	2 (5)
Human immunodeficiency virus	2 (5)
Diabetes	1 (3)
Renal insufficiency	1 (3)
Tuberculosis	1 (3)
Malaria at presentation — no. (%)	4 (11)
Symptoms — no./total no. (%)	
Fever	31/37 (84)
Fatigue	24/37 (65)
Diarrhea	23/37 (62)
Headache	12/21 (57)
Vomiting	21/37 (57)
Anorexia	16/37 (43)
Vital signs at admission	
Temperature — °C	38.6±1
Heart rate — beats/min	93±14
Systolic blood pressure — mm Hg	125±25
Median interval from onset of symptoms (IQR) — days	
To hospital admission	5 (3–7)
To death	8 (7–11)



- **37 pacientes**
- **Conakry (Guiné)**
- **Março/Abril 2014**

November 5, 2014 | E.I. Bah and Others
(DOI: 10.1056/NEJMoa1411249)



Avaliação de Fatores de Risco



Table 4. Characteristics of Survivors and Nonsurvivors.

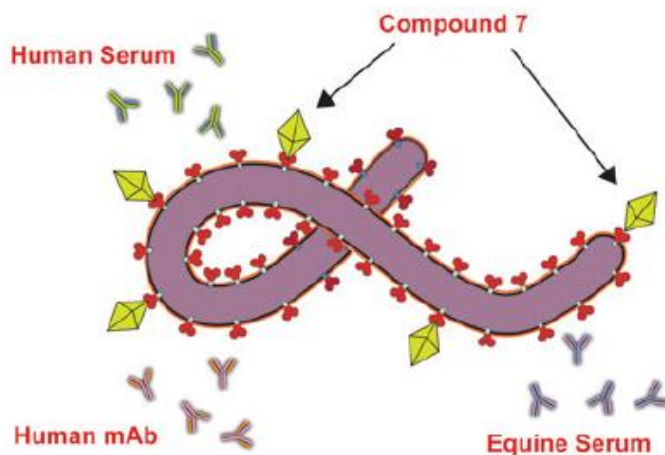
Characteristic	Survivors (N=21)	Nonsurvivors (N=16)	P Value
Median age (IQR) — yr	29 (26–37)	45 (40–47)	0.005
Male:female ratio	14:7	10:6	1.00
Viral load at admission			
Mean \pm SD — copies/ml	8207 \pm 17,189	68,361 \pm 111,340	0.02
Median (IQR) — copies/ml	1079 (148–5059)	1915 (141–12,998)	0.47
>100,000 copies/ml — no. (%)	0	4 (25)	0.02
Health care worker — no. (%)	6 (29)	8 (50)	0.31
Clinical features			
Hemorrhage — no. (%)			
Any visible	8 (38)	11 (69)	0.1
Gastrointestinal	4 (19)	6 (38)	1.0
Interval from symptom onset to presentation (IQR) — days	5 (4–8)	5 (2–7)	0.49

November 5, 2014 | E.I. Bah and Others
(DOI: 10.1056/NEJMoa1411249)

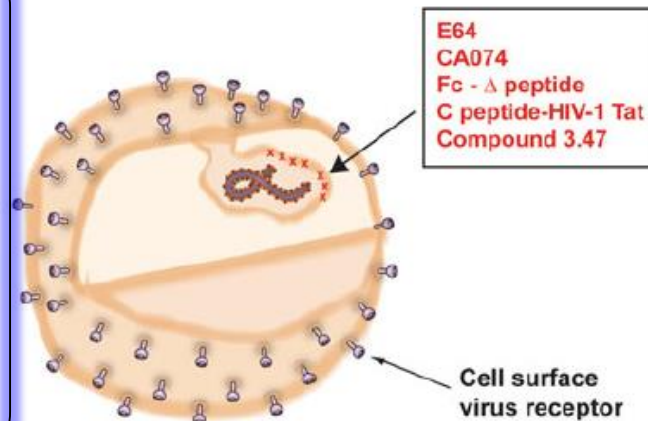
Tratamento



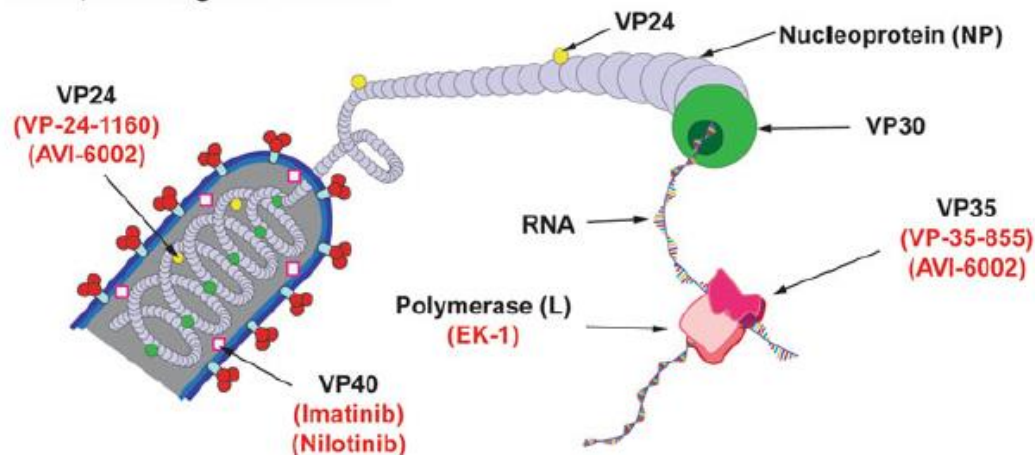
A Cellular entry



B Endosomal escape



C Virus Replication, Budding and Release





Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks

**Interim Guidance for National Health Authorities and Blood
Transfusion Services**

Version 1.0 September 2014



**World Health
Organization**

**Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from
Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks**

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1 Introduction

2 Guidance on donor selection, screening, donation and handling of blood and plasma units

- 2.1 Identification of suitable blood or plasma donors among patients recovered from
Ebola viral disease (EVD)
- 2.2 Donor information, consent and selection
- 2.3 Donor's blood grouping and TTI screening
- 2.4 Blood collection and donor care
- 2.5 Storage of whole blood and plasma units, inventory management and transportation

3 Guidance on transfusion of convalescent whole blood or plasma

- 3.1 Selection of EVD patients
- 3.2 Informed consent
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- 4.3 Data collection, analysis and interpretation

Annexes

Annex 1: Example of a consent form for donation of convalescent whole blood or plasma
to treat Ebola virus disease

Annex 2: Example of a consent form for treatment with experimental convalescent whole
blood or plasma therapy

Annex 3: Example of a Data Collection Form: Treatment with convalescent whole blood
(CWB) or plasma transfusion (CP)



Transfusão de Sangue



- 8 pacientes tratados com transfusão de sangue de pacientes convalescentes durante surto de DVE na República Democrática do Congo em 1995

Table 2. Characteristics of 8 Ebola-infected female convalescent blood transfusion recipients.

Patient	Age (years)	No. of days between onset of symptoms and transfusion	Blood volume (cm ³)	Received blood from donor no.	Outcome
1	27	7	400	1	Survived
2	12	11	150	2	Survived
3	15	13	150	3	Survived
4	54	9	250	2	Survived
5	44	15	250	4	Survived
6	25	13	250	4	Survived
7	40	11	450	5	Survived
8	48	4	400	2	Died

The Journal of Infectious Diseases 1999;179 (Suppl 1):S18–23



ZMapp



- **Droga experimental: em desenvolvimento (2 laboratórios)**
- **Combinação de 3 anticorpos monoclonais (mAbs) contra GP**
- **Anticorpos produzidos em plantas: *Nicotiana benthamiana***
- **Sucesso em tratamento em PNH**

Zhang YF, et al. Sci China Life Sci October (2014) Vol.57 No.10

Qiu X, Wong G, Audet J, et al. Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp. Nature 2014;514:47-53



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Imunomoduladores e Moduladores de Coagulação



Table 3 Anti-viral compounds currently tested in non-human primate models of Ebola infection

Platform	Therapeutic targets	Prophylactic efficacy	Therapeutic efficacy	Concerns	References
Recombinant human activated protein C (rhAPC)	Abnormal coagulation	Not tested	Partial protection 2 mg/m ² /h (I.V. infusion) until day 7 post-exposure	Low efficacy, manipulation of coagulant pathway, withdrawn from global market (2011)	147
Recombinant nematode anticoagulant protein C2 (rNAPC2)	Factor VIIa: tissue factor complex	Not tested	Partial protection 30 µg/kg BW/day until day 14 post-exposure	Low efficacy, manipulation of coagulant pathway	146
Small interfering RNAs (siRNA)	L polymerase + VP24 + VP35	Not tested	Yes 2 mg/kg BW (7 doses)	Multiple doses required	123
Phosphorodiamidate morpholino oligomers nucleotides (PMOs) (LNP/siRNA: TKM-Ebola)	L polymerase + VP24 + VP35	Not tested	Yes 12.5 ~ 200 mg (11 doses)	Multiple doses required	128
Monoclonal neutralizing Antibodies (NABs)	Ebola Virion (KZ52)	No	No	No efficacy	103, 194
Triple monoclonal antibody cocktail	Ebola GP	Not tested	Full protection 24H, Partial Protection 48H 25 mg/kg BW (3 doses)	Multiple doses required, must be used early after exposure	106

BW body weight, *GP* glycoprotein, *LNP* lipid nanoparticle

BioDrugs (2013) 27:565–583

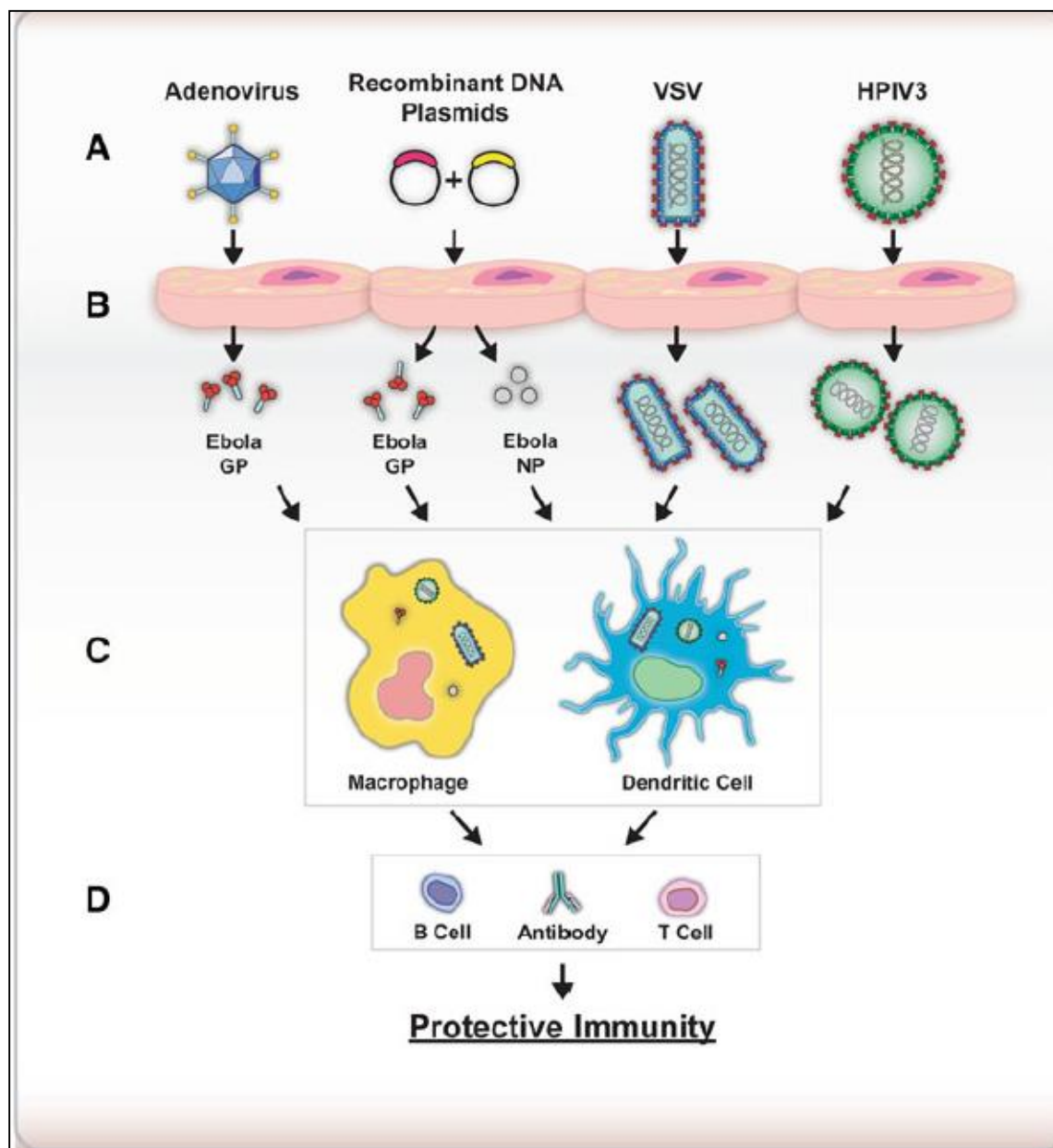


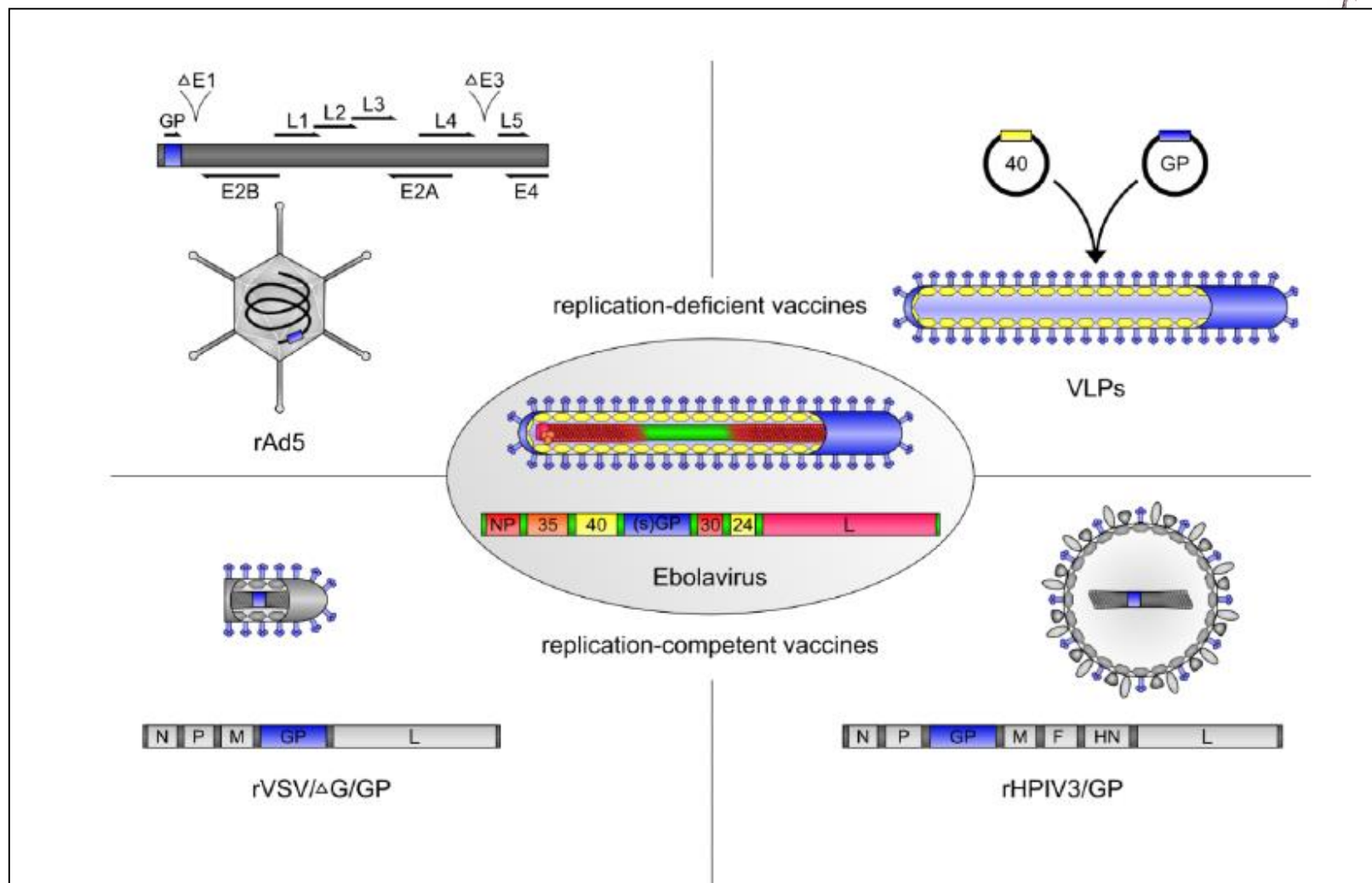
Vacinas



- **Alvo: proteínas EBV**
- **Vacinas: DNA /Recombinação Viral**

Característica	Surtos	Grupos de Risco
Proteção imediata	Essencial	Não é essencial
Imunização duradoura	Desejável, mas não essencial	Essencial
Proteção cruzada entre espécies	Desejável, mas não essencial	Essencial
Número de doses	Dose única	Múltiplas doses é aceitável







The NEW ENGLAND JOURNAL of MEDICINE



Perspective

Ebola Vaccine — An Urgent International Priority

Rupa Kanapathipillai, M.D., Ana Maria Henao Restrepo, M.D., Patricia Fast, M.D., Ph.D., David Wood, Ph.D., Christopher Dye, D.Phil., Marie-Paule Kiery, Ph.D., and Vasee Moorthy, B.M., B.Ch., Ph.D.

With the Ebola epidemic in West Africa continuing to grow, the World Health Organization (WHO) convened an urgent meeting on September 29 and 30 to assess the efforts under way to evaluate and

produce safe and effective Ebola vaccines as soon as possible.¹ The 70 scientists, public health officials, and representatives from industry and regulatory bodies who gathered in Geneva discussed two vaccine candidates at length — cAd3-EBOV (cAd3), from GlaxoSmithKline (GSK) and the U.S. National Institute of Allergy and Infectious Diseases (NIAID), and rVSVAG-EBOV-GP (rVSV), from NewLink Genetics and the Public Health Agency of Canada.

of rVSV soon. Both vaccine candidates have demonstrated 100% efficacy in studies in nonhuman primates,^{2,3} but how that will translate to human subjects remains unknown. The phase 1 trials of both vaccines use dose-response designs structured to determine the level of humoral and cellular immunity that can be induced. The minimum antibody titer needed to confer protection in humans is unknown. Because of the small numbers of partici-

the monovalent form is based on the Zaire strain of Ebola virus, which is the cause of the current West African epidemic, and the bivalent form includes the Sudan strain of the virus as well (see Fig. 1). The monovalent form will be evaluated in a nonrandomized, open-label study involving 60 adult volunteers who will receive the vaccine at three different doses (1×10^{10} vp, 2.5×10^{10} vp, and 5×10^{10} vp). The bivalent form will be evaluated in a nonrandomized, open-label study involving 20 adult volunteers who will receive the vaccine at two different doses (2×10^{10} PU and 2×10^{11} PU). Both studies will assess safety, side effects, and immunogenicity,

October 7, 2014 | R. Kanapathipillai and Others

(DOI: 10.1056/NEJMp1412166)



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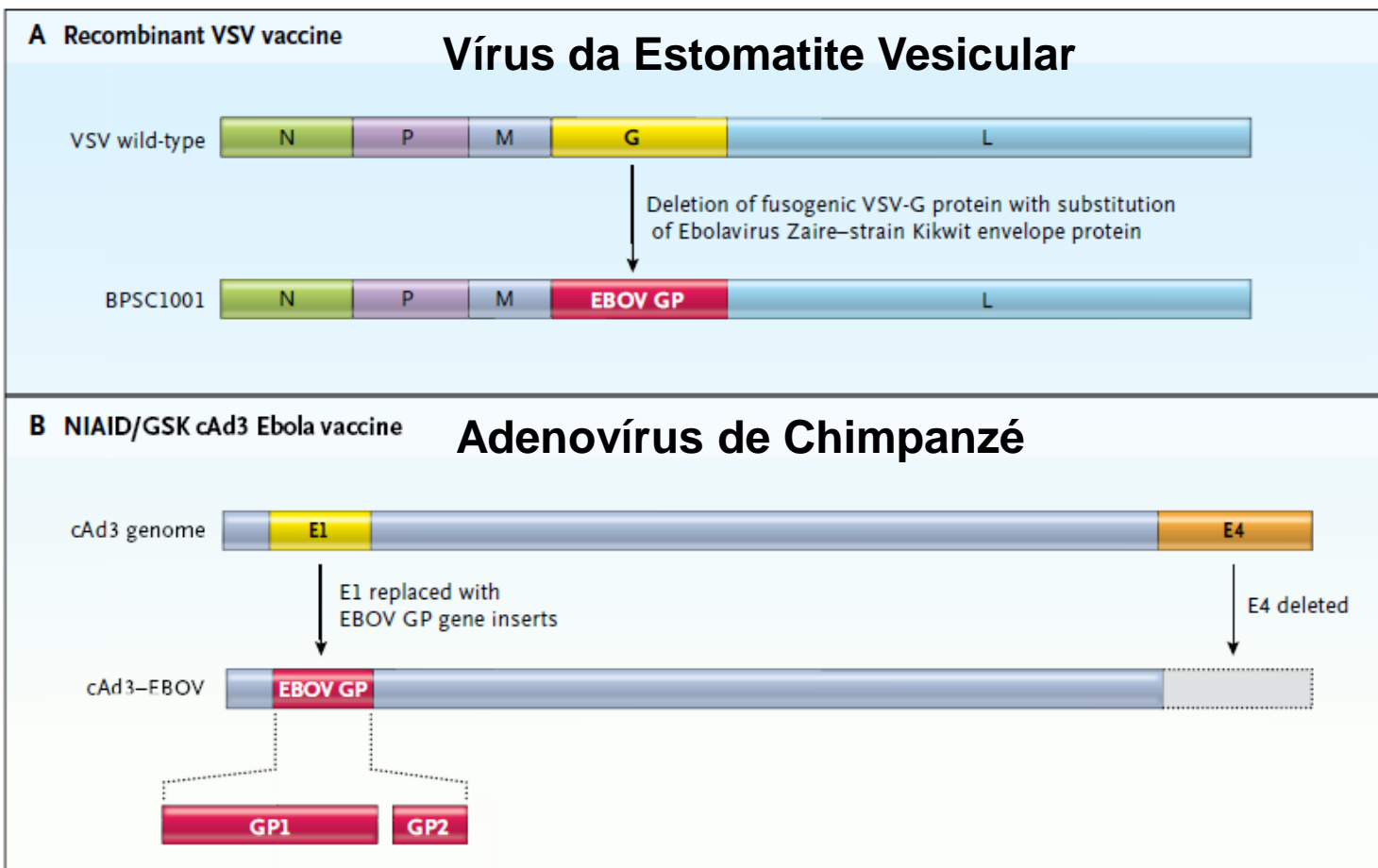


Figure 1. Structures of Ebola Vaccine Candidates rVSV (Panel A) and cAd3 (Panel B).

October 7, 2014 | R. Kanapathipillai and Others

(DOI: 10.1056/NEJMp1412166)



“A globalização pode gerar surtos de ebola em qualquer parte do mundo através da transmissão incidental. Assim, a descoberta de uma vacina assumiu maior urgência”

Ebola Virus: Immune Mechanisms of Protection and Vaccine Development.

Adeline M. Nyamathi, John L. Fahey, Heather Sands and Adrian M. Casillas

Biol Res Nurs 2003 4: 276



Obrigada!



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