Fractional dosing of Yellow fever vaccines: review of vaccine potency & stability information, available evidence, and evidence gaps

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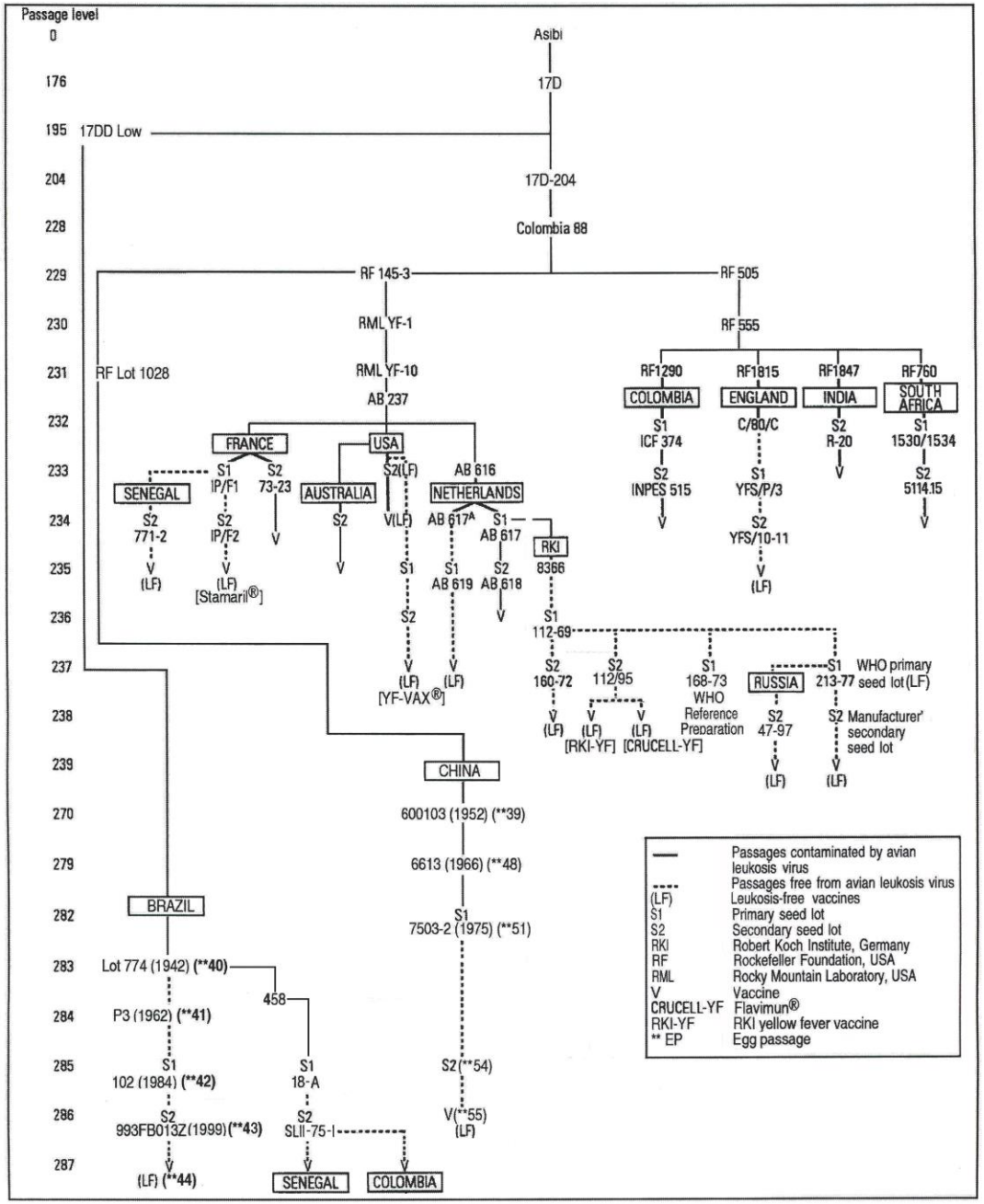
Review of vaccine potency & stability information

17D Genealogy

1. Asibi gave rise to 17D. 17D was then passaged in different labs to develop substrains 17D-204 17DD, and 17D-213.
2. 17D lineage is well described and tightly regulated, providing natural controls to the study.
3. Original 17D virus (p176) is not available.
4. Seed lot system controls passage level of commercial vaccine product.
5. 17D-204: All current.
6. 17D-213: RKI derived from 17D-204, ALV-free.
7. 17DD: Brazil only.



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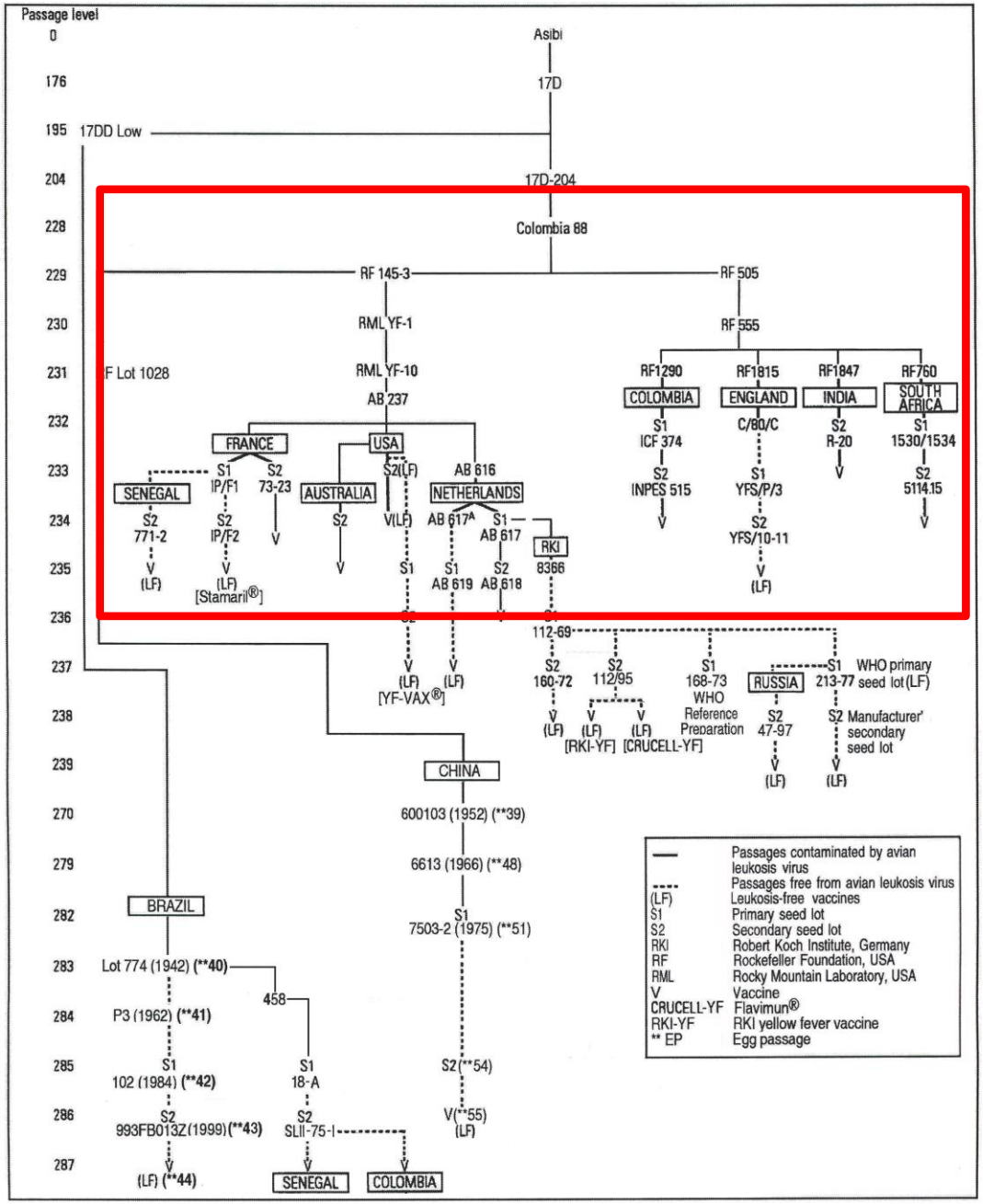

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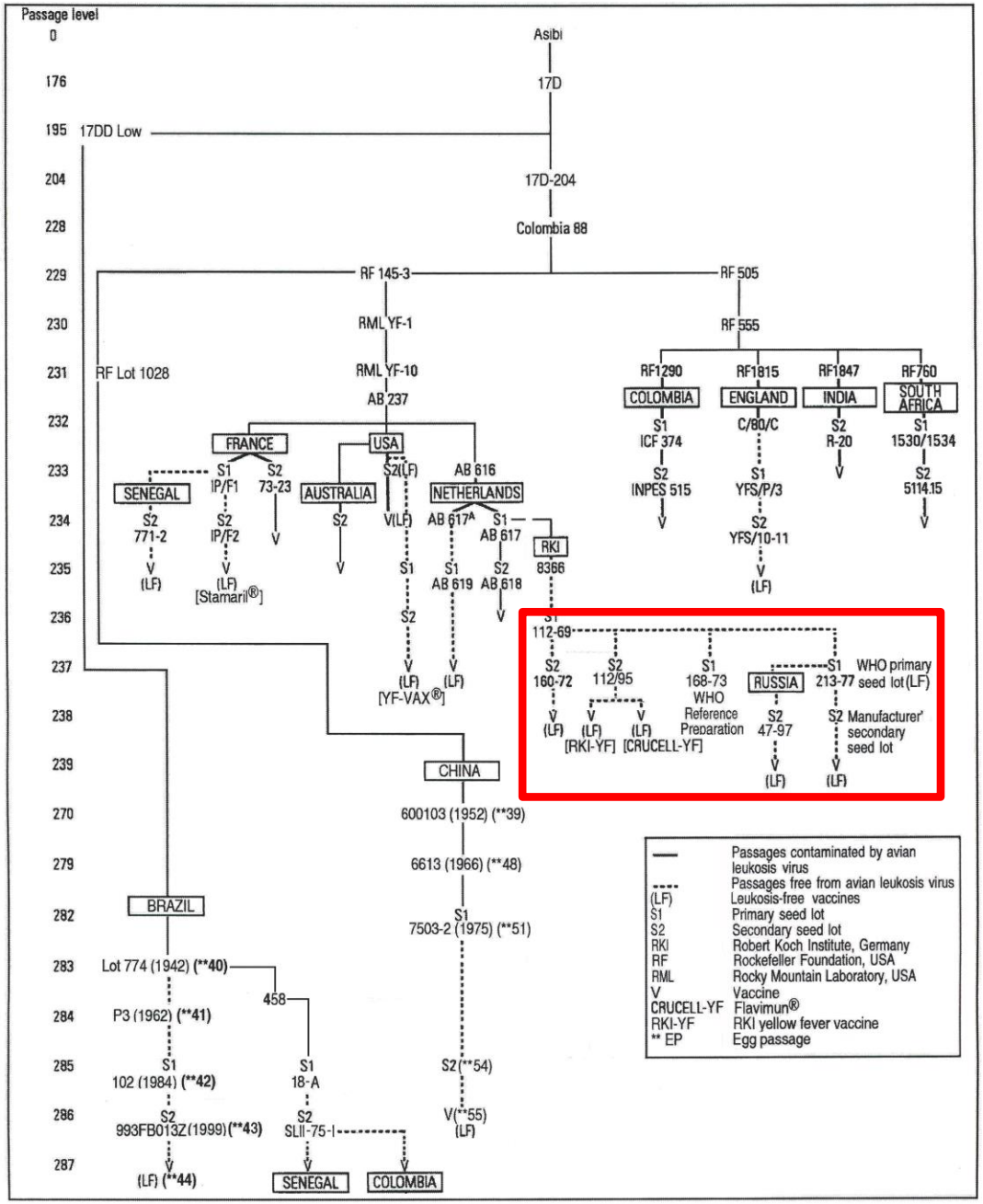

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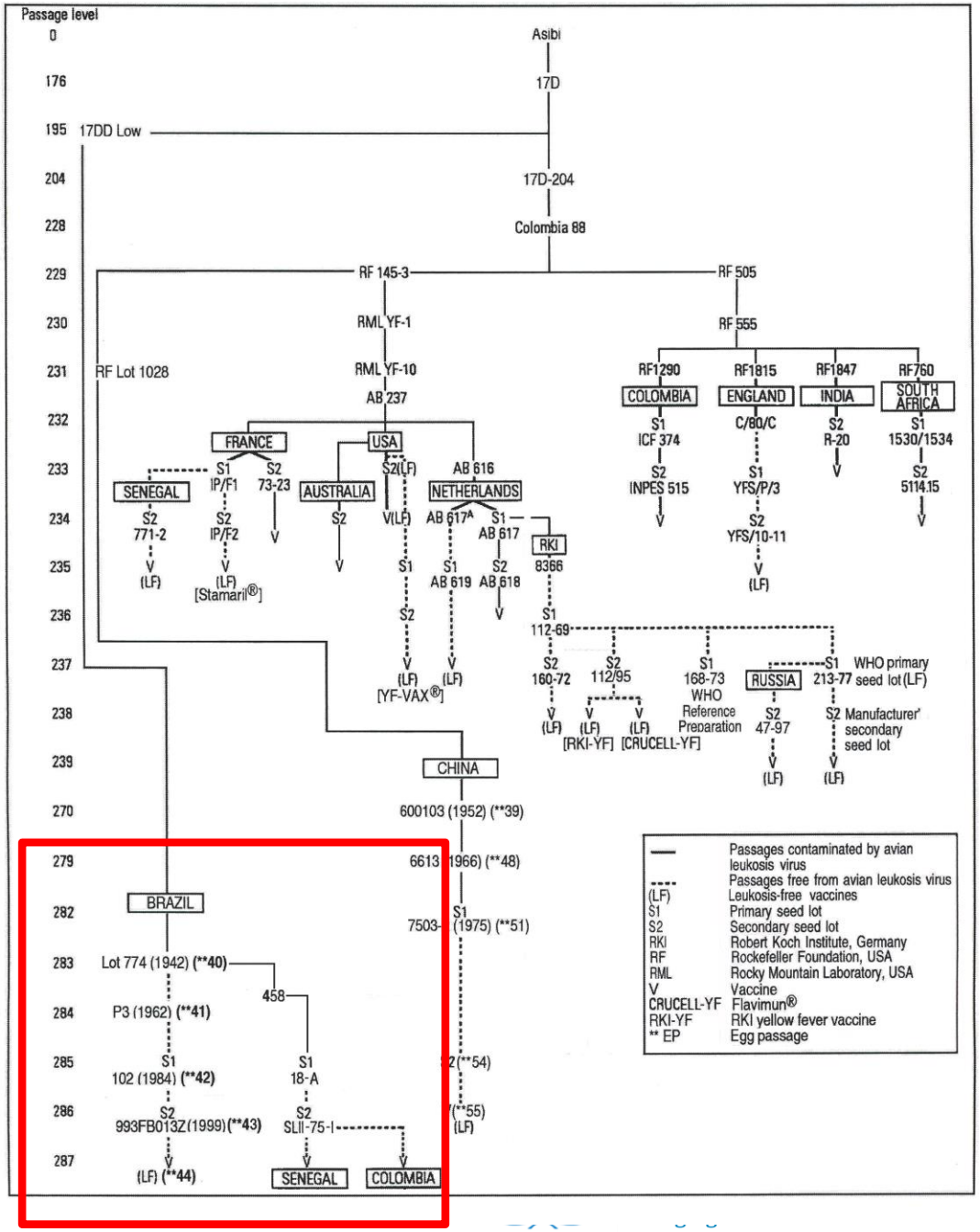

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17D vaccine manufactured by six producers

17D-204:

- China
- France
- Senegal
- USA

17D-213:

- Russia

17DD:

- Brazil

WHO Prequalified (PQ) vaccines

17D-204:

- China
- France – Sanofi Pasteur
- Senegal - Institut Pasteur Dakar
- USA

17D-213:

- Russia - Federal State Unitary Enterprise of Chumakov Institute

17DD:

- Brazil - Bio-Manguinhos

Batch records show variable potency between manufacturers

Batch potency (IU)	Manufacturer 1	Manufacturer 2	Manufacturer 3**	Manufacturer 4
Average	43651	25704	18977	12874
Maximum	114815	125896	177827	26284
Minimum	13490	3715	4169	7578
Average 1/5	8709	5129	4467	2569
Minimum 1/5	2692	741	832	1516

*The WHO requirements do not specify a maximum potency; only a minimum potency of 1000 international units

**reported in PFU; others reported in international units

Vaccine stability before reconstitution,
storage at 2-8°C, 10 dose vials

Average vaccine potency	Manufacturer 1 (IU)	Manufacturer 2* (PFU)	Manufacturer 3 (IU)	Manufacturer 4 (IU)
O years	19,054	34,674	91,201	20,417
2 years	7,079	14,791	74,131	14,791
3 years	21,876	14,791	46,773	16,218

*Reported in PFU; others reported in international units IU

Available evidence for dose sparing

Limited number of dose response studies

Characteristics	Lopes et al. 1988	Roukens et al. 2008	Martins et al. 2013*	Campi-Azevedo et al. 2015*
Vaccine	Bio-Manguinhos	Sanofi Pasteur	Bio-Manguinhos	Bio-Manguinhos
Subdose	Four dilutions down to 1/1000 SC	1/5 full dose ID	Down to 1/46 of full dose SC	Down to 1/46 of full dose SC
Sample size	259 males	175 adults	749 males	749 males
Follow-up	28D	1Y	10 months	1Y
Readouts	Seroconversion	Seroconversion	Seroconversion	Viremia, cytokines & chemokines

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* Same study with different analyses

Clinical observations on dose-sparing strategies for YF vaccine

Lopes et al. (1988) did dose finding study using four dilutions of four lots

- 1 in 10, 1 in 60, 1 in 100, and 1 in 1000
- Full seroconversion down to 200-500 pfu/dose dilution in various vaccine lots

Roukens et al (2008) studying the ID administration of YF vaccine

- Participants received 0.1 ml (1/5th of full dose) ID or 0.5ml SC.
- 2 weeks to 1 year after vaccination equivalent seroprotective titres of 1/5th ID to 1/1 SC vaccine administration were achieved. Not validated in IU.

Martins (2013) & Campi-Azevedo (2014) studying SC vaccine administration

- Equivalent humoral response 46x dilution vs full dose, but only equivalent CMI response down to 9x dilution. Seroconversion in 97% of the participants at 30 days.

Summary of Brazilian studies

- 17DD vaccine;
- 749 adult males in the army; double blind, randomized clinical trial to test for immunological non- inferiority, over 12 months.
- Full dose of 27,476 IU compared to five lower formulations
  - 10,447 IU
  - 3,013 IU
  - 587 IU
  - 158 IU,
  - 31 IU
- Seroconversion: 97% (except fractions lower than 587 IU).
- No serious adverse events were reported from any groups.
- Also differences seen in pro inflammatory (TNF, IFNγ, IL-2) and modulatory cytokines (IL-5, IL-10) when moving below 3013 IU; unclear what happens between 3013 iu and 587 IU
- Analysis of serum cytokines/chemokines in association to PRNT and viremia, support 10-fold lower subdose (3013 IU) of vaccine.

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- Differences seen in pro inflammatory (TNF, IFNγ, IL-2) and modulatory cytokines (IL-5, IL-10)as well as viremia profile when moving below 3013 IU; unclear what happens between 3013 IU and 587 IU
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Evidence gaps

Data limitations

- Recent studies only undertaken with vaccine from Brazil.
- No equivalent studies with three other PQ vaccines.
- Important as Brazil is 17DD substrain while other three PQ vaccines are 17D-204/17D-203 substrain.
- No pediatric population included in the studies to evaluate immunogenicity and safety.
- Similarly, no data available for immunocompromised subjects
- Study populations not representative for flavivirus exposure, genetic background and sex.
- Long-term duration of immunity beyond one year is unknown using a dose-sparing approach.
- No assessment of rare adverse events due to limited sample size.

Conclusions

- YF vaccine a “legacy” vaccine produced in embryonated chicken eggs.
- Similarly, requirements for minimum amount of virus in a dose of 1000 international units [IU] is based on historic animal and data field experience.
- Potency of vaccine produced by the four PQ manufacturers largely exceeds minimum potency requirement but is highly variable.
- Fractional dose YF vaccination (volume reduction) can be done while maintaining vaccine potency above the minimum level.
- Studies to date suggest that fractional dose down to 600IU via IM/SC shows similar immunogenicity as the full dose, and similar cytokine and viremia profile down to 3000 IU.
- No data are available from populations that have been associated with somewhat reduced seroconversion rates, such as young children, immunocompromised subjects and pregnant women.
- Additional data needed to support 1000 IU as minimum potency.