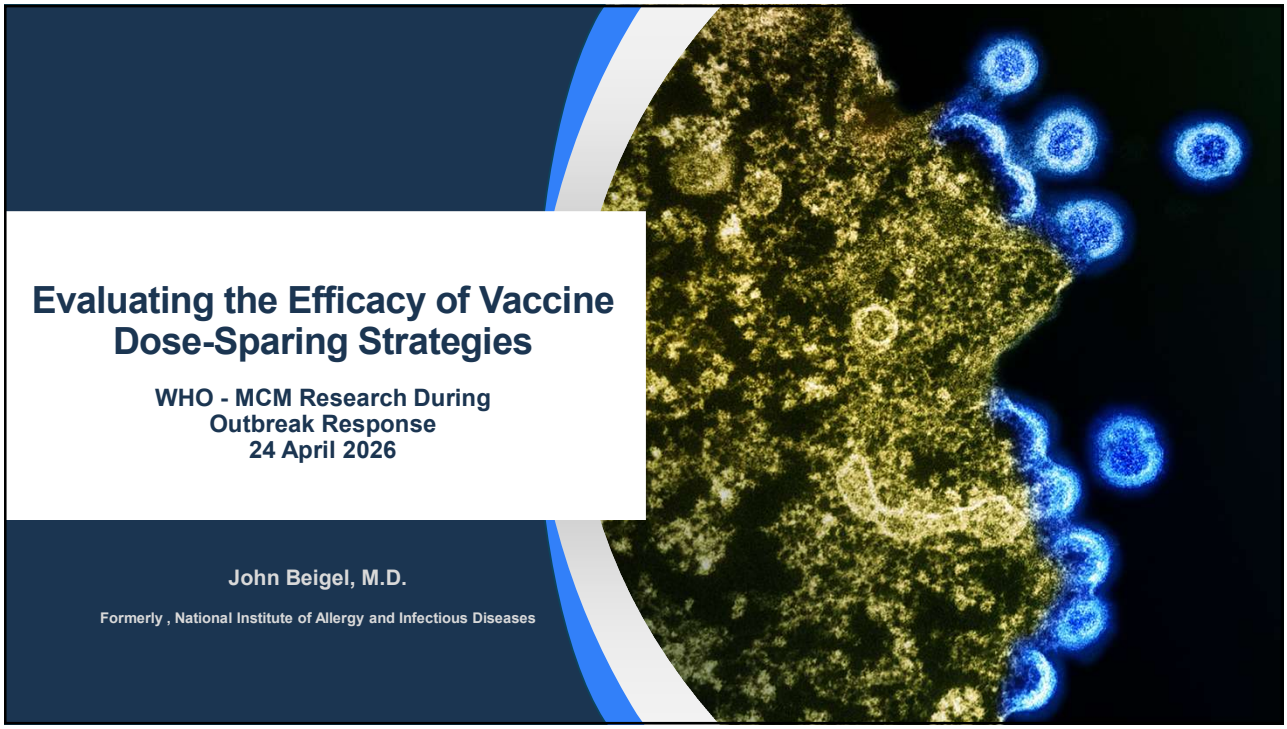

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When to Consider Dose Reduction Strategies

Demand exceeds supply

- Outbreak response (e.g., stockpile limitations)

Cost reduction / improved resource allocation

- Particularly relevant for global immunization programs

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When Dose Reduction Is Less Useful

Not well suited for initial vaccine development

- Dose selection already explored in Phase 1/2 trials

Phase 3 trials

- Evaluating multiple doses increases complexity and delays timelines

Comparative clinical efficacy studies

- For highly effective vaccines, non-inferiority trials using clinical endpoints require very large sample sizes

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Examples of Dose Reduction Strategies

Modified Vaccinia Ankara-BN

- Route change (ID): ~1/5 standard dose (evaluated down to 1/10)
- Used under Emergency Use Authorization for mpox in the U.S.

Yellow Fever Vaccine

- Same route (dose reduction): ~1/5 standard dose
- Used in outbreak response (e.g., 2016 Democratic Republic of the Congo yellow fever outbreak)

Other Relevant Examples

- True fractional (reduced antigen per dose):
  - Inactivated polio vaccine (intradermal)
  - Rabies vaccine (intradermal)
  - Influenza vaccines (intradermal)
  - COVID-19 vaccines (e.g., half-dose boosters)
- Schedule reduction:
  - Cholera vaccines (fewer doses)
  - HPV vaccines (fewer doses)

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Dose Reduction is Most Successful When One of the Following Applies:

1. Highly immunogenic platforms

- Especially those of live attenuated vaccines (e.g. yellow fever) without preexisting immunity

2. Intradermal delivery feasibility

- Enables lower antigen doses by the high density of antigen-presenting cells in the dermis
- Examples:
  - MVA-BN
  - IPV
  - Rabies

⚠️ Limitation: Requires training, specialized devices, and may affect tolerability

3. Schedules (2+ doses) originally driven by immunogenicity

- e.g., HPV vaccines
- Opportunity to reduce:
  - Number of doses
  - Possibly antigen per dose

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Trial Design Considerations

Is there a validated immunologic correlate of protection?

- Critical requirement for immunogenicity-based non-inferiority
- Example:
  - MVA-BN approval leveraged PRNT titers vs ACAM2000, so precedent for using PRNT titers for dose sparing

Endpoint selection

- Preferred:
  - Functional assays (e.g., PRNT)
  - Neutralizing antibody titers
- Not typically used/accepted as primary endpoints:
  - T-cell responses
  - Composite or longitudinal antibody measures

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Trial Design Considerations

Timing of immunogenicity assessment

- Typically:
  - Peak response after last dose (e.g., MVA-BN: 2 weeks after 2nd dose)
- Risks - misses differences in:
  - Early protection
  - Durability

Non-inferiority design

- Typical criterion:
  - Lower bound of 95% CI for GMT ≥ 0.67

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Trial Design Considerations

Durability considerations (often under-addressed)

- Fractional dosing may:
  - Preserve peak titers
  - May result in faster waning of immunity
  - ⚠️ Non-inferior peak titers do not guarantee durability of protection
- Trials are rarely powered for long-term follow-up comparisons

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Operational / Strategic Considerations

Manufacturers may have limited incentives for dose sparing

- A lower dose may lead to lower revenue
- Similar or increased costs: additional studies, supply chains, regulatory costs, etc.
- Public health value and manufacturer incentives may diverge
- *Example: For MVA-BN, the intradermal strategy advanced without full manufacturer support. NIAID held IND for trials, and submitted the request and data supporting EUA,*

Route changes (especially intradermal) may be:

- Less acceptable
- Operationally complex (more training, different supplies, etc.)

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Conclusions

Fractional dosing is a proven strategy to extend vaccine supply and should be considered during outbreak response

It is most viable when supported by immunologic correlates but remains constrained by durability, logistics, and incentives

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