Lessons learned from the implementation of a CCHF vaccine in Bulgaria and what an ideal CCHF vaccine would look like

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Bulgarian CCHF vaccine (inactivated)

- The only currently available CCHF vaccine
- Since 1974
- CCHFV cultivated in suckling mouse brain, inactivated by chloroform, heated at 58°C and absorbed on Al(OH)₃
- Vaccine CCHFV strain v42/81 – 1981
- Vaccine strain and CCHFV strains from Bulgarian patients cluster together in the “Europe 1” clade: mean genetic difference in the S-, M- and L- segment – 2.2%, 6.2% and 3.3% resp.
Indications

To prevent CCHF by immunization of target groups over 16-year age
- military and medical personnel
- farmers
- other persons living or working in CCHF endemic regions of Bulgaria
Dosage

✓ At day 0 and 30 days later, subcutaneously

✓ Reimmunization – 1 year after the first application

✓ Every 5 years after the first reimmunization
Bulgarian Ministry of Health:

4-fold reduction in the number of reported CCHF cases was observed over 21-year period following initiation of vaccination

1953-1974: 1105 CCHF cases, case fatality rate 17%
1975-1996: 279 CCHF cases, case fatality rate 11.4%

multiple factors
Mehrdad Mousavi-Jazi, Helen Karlberg, Anna Papa, Iva Christova, Ali Mirazimi. Healthy individuals’ immune response to the Bulgarian CCHFV vaccine *Vaccine, 2012*

The first detailed analysis of the **cellular and humoral** immune response

Blood samples of:

- 4 individuals with several vaccinations
- 4 individuals with completed one vaccination program
- 6 healthy people as a control group

- IFN-γ ELISpot assay to monitor IFN-γ-secreting T-cells
- ELISA for IgG anti-CCHFV antibodies against CCHFV glycoprotein and nucleoprotein
- microneutralization assay
Bulgarian CCHFV vaccine induces T-cell response against CCHFV nucleoprotein
- frequency of IFN-γ-secreting T-cells was 10-fold higher in individuals with reimmunizations compared with those with only one vaccination program

CCHFV vaccine induces specific antibody responses
- strong IgG antibody response in all
- antibody titer 200-3200 in multi-vaccinated individuals and 200-800 in single-vaccinated

Low neutralization activity
- 2 to 4-fold higher in multi-vaccinated than in single-vaccinated individuals

Booster vaccinations are required to confer protective immunity
What an ideal CCHFV vaccine would look like

- Induction of both, T cell and humoral, immune response (expression of large gene segments)
- Neutralization activity of antibodies
- no need of adjuvants
- safety
- 100% efficacy in mice
- thermostable (no need to maintain the cold chain)
DNA vaccines

- DNA plasmids expressing CCHFV proteins
- DNA vaccine expressing M-genome
  + neutralizing antibodies against Gn and Gc
  - 60% efficacy (IFNAR mice)

- DNA vaccine coding Gc, Gn and NP
  + induction of both humoral and cell-mediated immune response
  + complete protection in mice

- DNA vaccine coding NP (S)
  - adjuvant: CD24 protein
  + humoral and cellular immune response
  - no neutralization activity of antibodies
  + protection of IFNAR mice

Garrison A. et al. *PLOS Neglected Tropical Diseases*, 2017
Farzani T. et al. *Viruses*, 2019
Viral vectors: Modified Vaccinia virus Ankara

Poxvirus vector + inserted M-segment (GP-encoding)
+ high-level gene expression of recombinant antigens
+ T cell and humoral immunity
+ no need of adjuvants
+ proven safety (in smallpox eradication)
+ 100% efficacy in mice (the only CCHF vaccine)
+ thermostable (no need to maintain the cold chain)

Buttigieg K. et al. *PLOS ONE, 2014*
Viral vectors: Adenovirus vaccine

- Human Adenovirus serotype 5 + inserted M-segment (GP-encoding)
  + T cell and humoral immunity (expression of large gene segments)
  - no protection in A129 mice (potentially could in STAT-1 mice)
  - high levels of pre-existing immunity (40-80% of adults)
    - chimpanzee adenovirus is an alternative (still 4-20% of adults have neutralizing antibodies)

  Sahib MM. et al. Canada, 2010

- Human Adenovirus serotype 5 + inserted NP-coding region (S-segment)
  + T cell and humoral immunity (expression of large gene segments)
  - partial protection – efficacy 78% IFNAR mice

  Zivcev M. et al. PLOS Neglected Tropical Diseases, 2018
**Viral vectors:**
**Bovine herpesvirus vaccine**

- Recently, Bovine herpesvirus type 4 – NP (S)
  + avoids pre-existing immunity problem
  + easy propagation in cell cultures
  + simple genome with a large capacity for inserting foreign genes
  + elevated cytokine levels and specific antibody response in BALB/c mice
    - unable to neutralize CCHFV in vitro
    - 75% protection rate

Farzani T. et al. *Viruses*, 2019
Subunit vaccines

- Ectodomains of Gn and Gc
  + induce neutralizing antibodies
  - no protection of STAT-1 mice


- Virus-like particles (VLP)
  Result of the self-assembly of recombinant viral proteins
  + similar antigenicity to the native virus
  + induction of strong humoral (neutralizing) and cellular immune response
  - transcriptionally competent VLP system with surface Gn and Gc, a minigenome encapsidated by NP and bound by viral polymerase
  + protection of mice from lethal challenge
  + no need of adjuvant

THANK YOU!