Serology and Immunology Capacity Building

Douglas R. Lowy, M.D.
Principal Deputy Director

3rd Virtual Meeting of the Frederick National Laboratory Advisory Committee

May 21, 2020

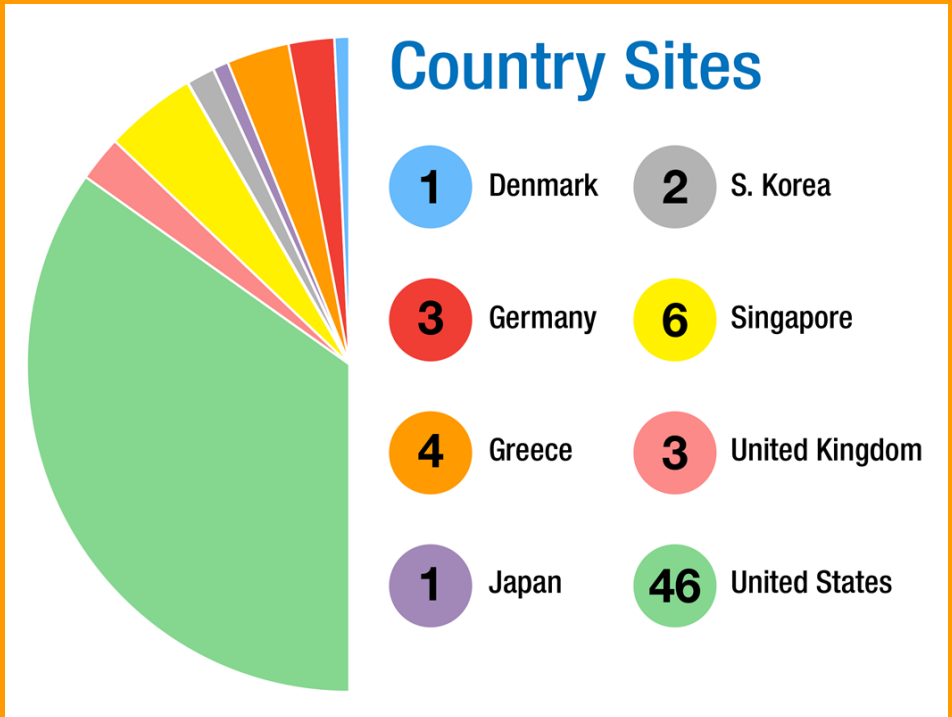
Topics for today

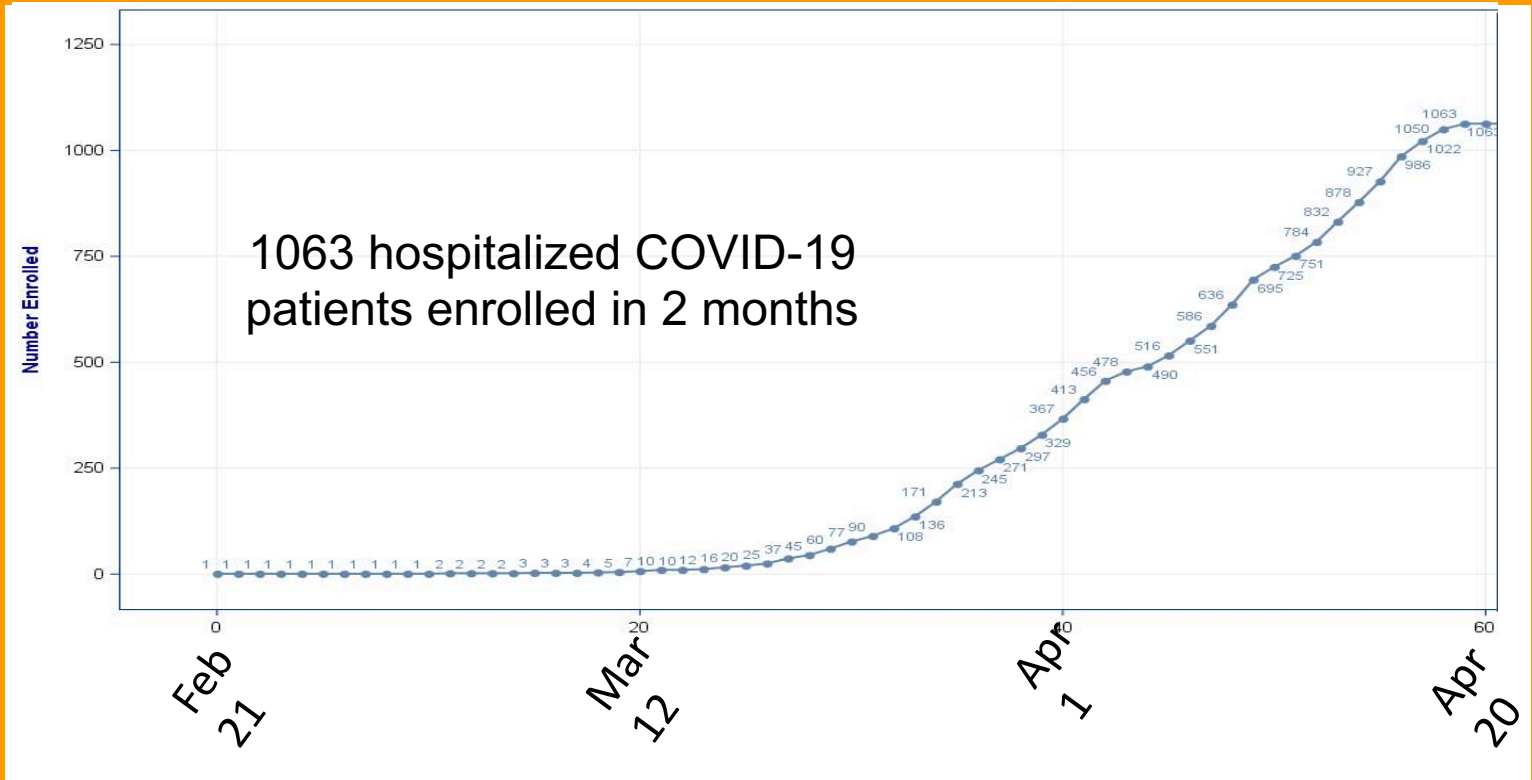
- Use of FNLCR by NIAID to respond rapidly to epidemics
- Use of FNLCR expertise in serology as an NCI response to COVID-19 epidemic
  - Pivoting the HPV serology laboratory to SARS-CoV-2 serology
  - Assisting the FDA in evaluating commercial SARS-CoV-2 serology devices
  - Why SARS-CoV-2 serology matters now and may become even more important in the future

NCI and NIAID are the major users of FNLCR

- **NIAID has made extensive use of FNLCR in responding rapidly to other epidemics:** Examples include SARS (2003), Ebola (2013), Zika (2015)
- **One example from current SARS-CoV-2 epidemic:** Developing a global therapeutic trial of **Remdesivir** in COVID-19 patients
  - A nucleoside analog, functions as an RNA chain terminator
  - Originally developed for treatment of Ebola and Marburg virus infections
  - Subsequently found to inhibit replication of other RNA viruses, including coronaviruses

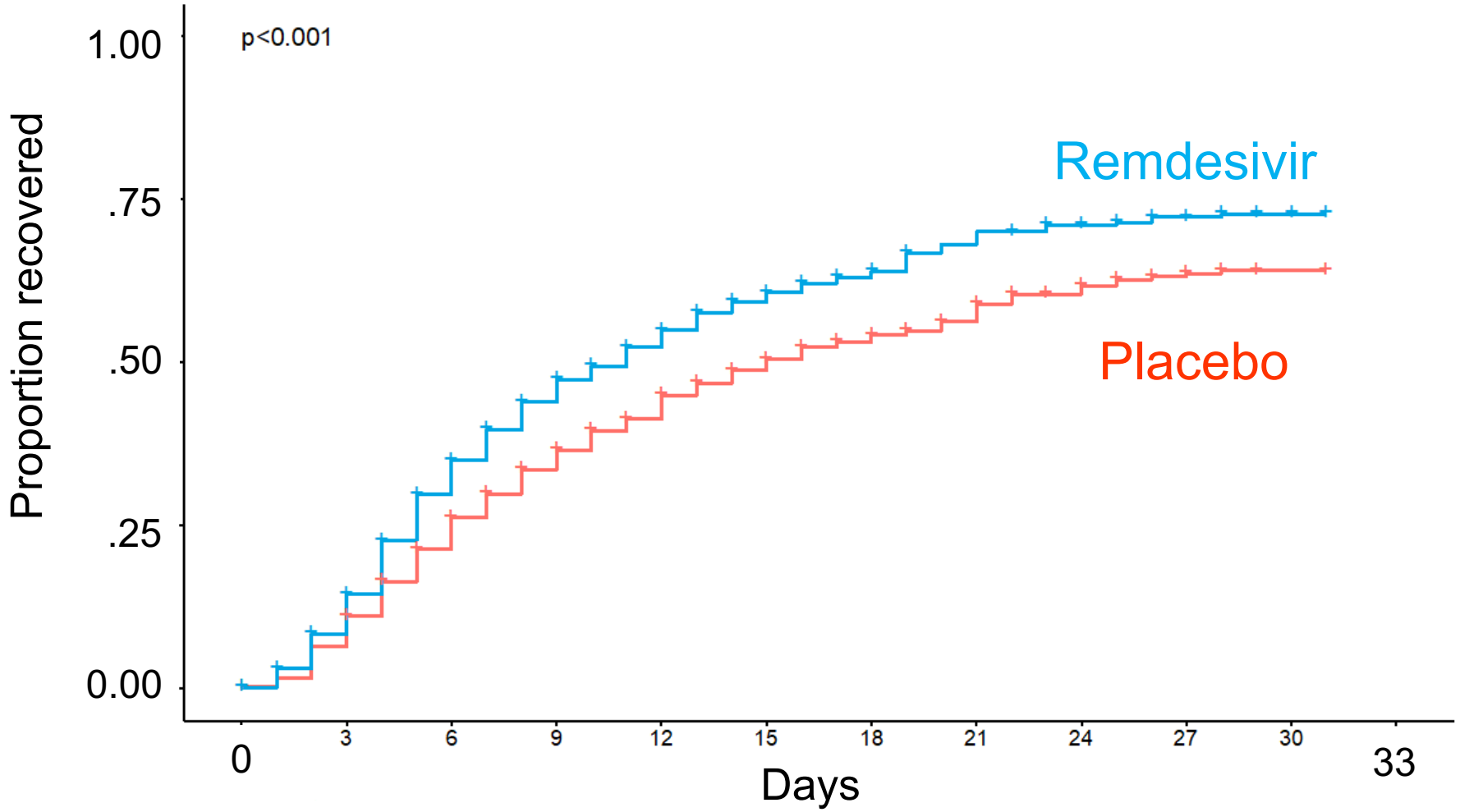
Adaptive Coronavirus Treatment Trial





Thanks to Cliff Lane, NIAID.

Hospitalized COVID-19 patients on Remdesivir treatment were discharged 31% faster than patients on placebo



Thanks to Cliff Lane, NIAID.

Lower 14-Day mortality rate for Remdesivir group than placebo group, but difference did not achieve statistical significance (p=0.059)

Treatment Group (Number Enrolled)	Deaths	%	Hazard Ratio	
			Estimate	95% CI
Remdesivir (538)	**32**	**7.1%**	**0.70**	**(0.47, 1.04)**
Placebo (521)	**54**	**11.9%**		

% is from the Kaplan-Meier estimate

28-day mortality data still being collected

Thanks to Cliff Lane, NIAID.

Convert part of HPV serology lab to SARS-CoV-2 serology

A collaborative research effort with several groups: NIAID, FDA, CDC, Mt. Sinai, others

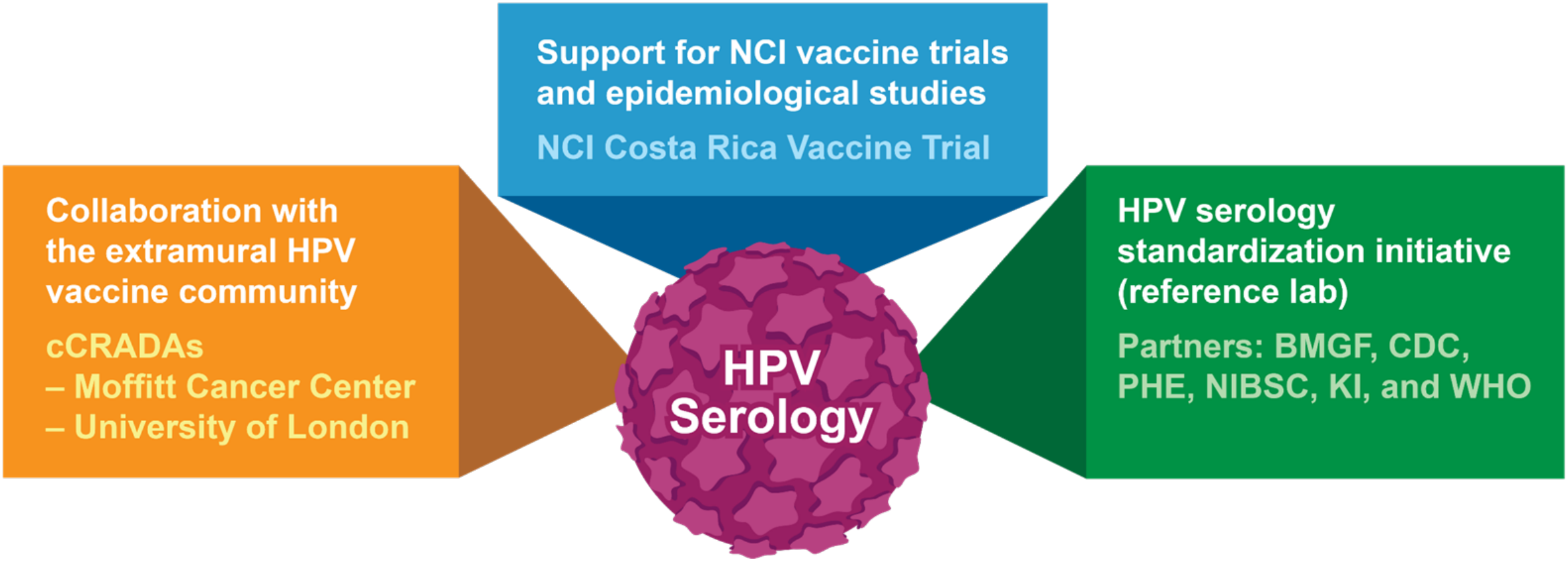
Shorter term goals:

1. Characterize performance of different serologic assays, correlate with neutralization assays, understand possible cross-reacting sera from prior to epidemic;
2. correlations with serologic tests submitted to FDA

Longer term goals: Understand implications of being seropositive (e.g., resistance to reinfection), duration of seropositivity

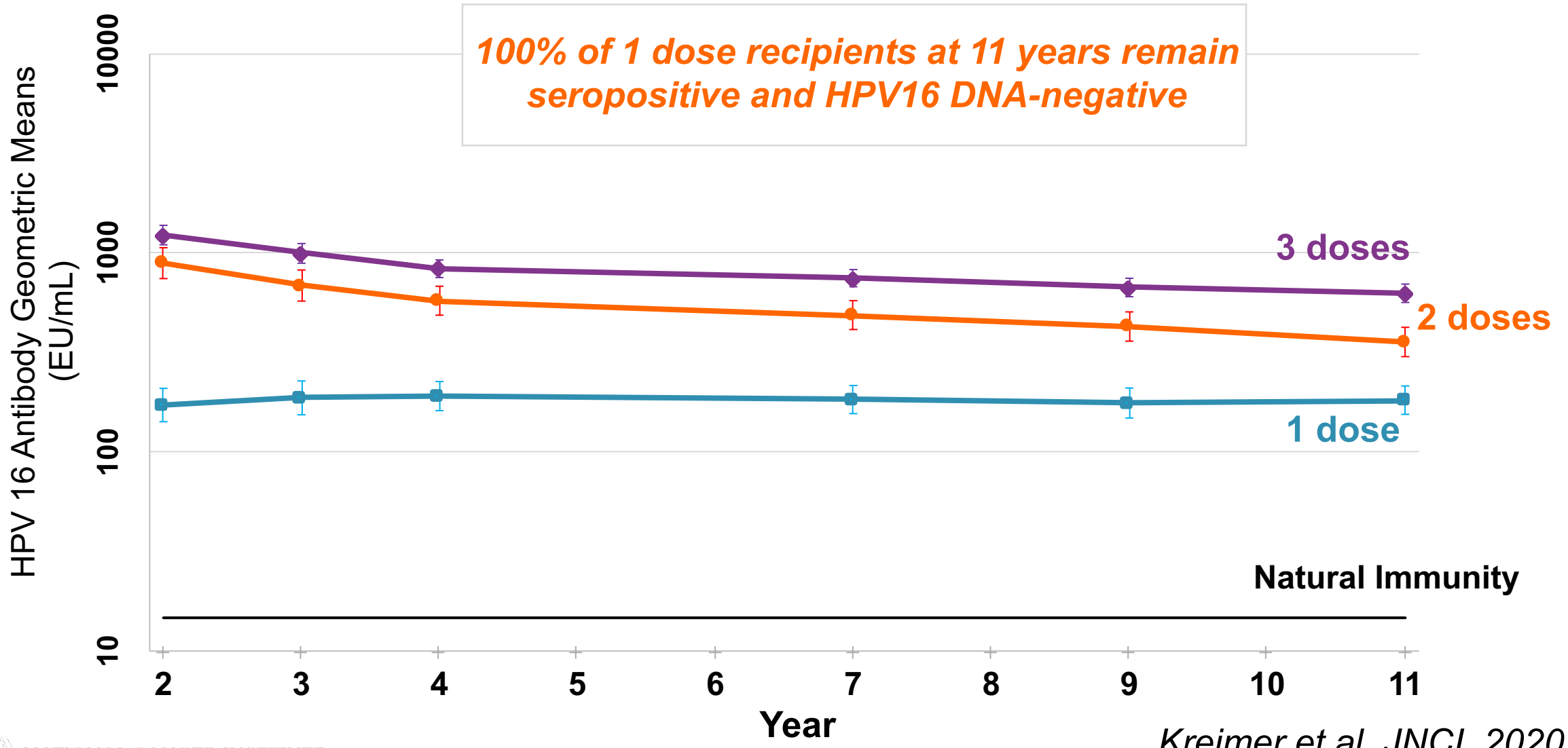
Cohort oriented research projects: COVID-19 longitudinal trial of cancer patients, others

FNLCR HPV Serology Activities



Thanks to Ligia Pinto, FNLCR

Stable HPV16 serum antibodies 11 years after one dose of the bivalent HPV vaccine (post-hoc analysis)



Kreimer et al, JNCI, 2020

The HPV Serology Laboratory - 2017

Sponsored by NCI and The Bill & Melinda Gates Foundation

HPV Serology Lab
Advancing HPV Assay Standardization

Mission:

- To work in **partnership** with the **international** HPV serology community to **promote further standardization, harmonization and proficiency of HPV serology assays** to assess vaccine immunogenicity in vaccine trials through:
  - development of **qualified assay standards**, **critical reagents** (HPV Virus-Like Particles), **multiplex assays and guidelines** available to the scientific community, and conduct **high-throughput testing** in clinical trials

Impact:

- Enable comparisons of data between different vaccines and studies
- Accelerate implementation of new vaccines and new vaccine recommendations

Partners:
Frederick National Laboratory: ***Ligia Pinto, Troy Kemp***
NCI: Doug Lowy, John Schiller, Sean Hanlon
The Bill and Melinda Gates Foundation: Peter Dull
CDC: Elizabeth Unger
Public Health England: Simon Beddows
Karolinska Institute: Joakim Dillner
Biostat Consulting, LLC: Brian Plikaytis
National Institutes of Biological Standards and Control (**NIBSC**): Dianna Wilkinson

Collaborators: Academic Labs, Vaccine Industry Labs, National Institutes for Food and Drug Control (NIFDC), WHO

HPV Serology Standardization: Main Aims

1. Development of secondary assay standards and a bank of serum specimens to use as assay proficiency panels for the 9 HPV types included in the licensed HPV vaccines
2. Production of qualified reference Virus-Like Particles (VLPs)
   - Develop a set of criteria to establish guidelines for qualification
3. Development and validation of a multiplex serology assay to support immunogenicity monitoring in HPV vaccine trials
4. Promotion of the use of standards (meetings, publications, data and protocol sharing)

Enable comparisons of data between different vaccines and studies

Accelerate implementation of new vaccines and new vaccine indications

"No one wants to have COVID-19, but everyone wants to have had it."

Maura Judkis
Washington Post
May 7

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Longer term goals

Understand implications of being seropositive (e.g., resistance to reinfection), duration of seropositivity

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FDA and commercial SARS-CoV-2 serology devices

- **March 16:** FDA permits sale of commercial laboratory-based and rapid lateral flow SARS-CoV-2 serology devices without its own assessment of their performance
  - Serology devices are not used to diagnose current infection; devices that measure viral RNA or viral protein are used to to diagnose current infection
- **May 4:** Emergency use authorization (EUA) by FDA has been given to several commercial devices; FDA requires all other manufacturers to submit EUA requests within 10 business days (May 18)

“The Wild West of COVID-19 antibody tests needs a sheriff.”

Lionel Laurent

Seattle Times and others

May 11

Summary of initial 20 commercial serology devices evaluated by FNLCR serology laboratory (taming the wild west)

- Focus on IgG antibody tests; IgM becomes positive at about the same time as IgG and decreases faster than IgG
- **Sensitivity** (detect true positives): Varies from 30% to 100%
- **Specificity** (does not detect false-positives): Varies from 87% to 100%
- Results sent to FDA; to help FDA determine suitability for EUA; FDA plans to make NCI evaluation results publicly available in near future
- In near future, only devices with high sensitivity and high specificity should be available

Importance of specificity at low rates of seroprevalence

- If a test has 99% specificity and the seroprevalence rate is found to be 5%,
  - **20% of the positives will be false-positives**

- If a test has 95% specificity and the seroprevalence rate is found to be 5%,
  - **50% of the positives will be false-positives**

Seropositivity: characteristics and questions

- Being antibody-positive means either the person is currently infected with SARS-CoV-2 or has been previously infected
- Can be used now for seroprevalence studies; should identify people who had asymptomatic or symptomatic infection
- It is not currently known: 1) whether being antibody-positive is associated with protection against reinfection; 2) what antibody levels may be associated with protection; 3) how long protection will last
- For candidate SARS-CoV-2 vaccines, will induction of neutralizing antibodies confer protection?

Thanks to

- **Ligia Pinto, Troy Kemp, Jim Cherry: NCI Frederick Serology lab**
- Cristina Cassetti, Hilary Marston, Maureen Beanan, Barney Graham, Kizzmekia Corbett: NIAID
- Michele Owen, Natalie Thornburg: CDC
- Rosemary Humes: BARDA
- Steve Gitterman, Brendan O'Leary, Jeet Guram: FDA
- Florian Krammer, Carlos Cordon-Carlo: Mt. Sinai Medical Center
- Mike Busch: Vitalant