Progress towards an HCV vaccine among people who inject drugs: What have we learned to inform HCV, COVID-19, and other emerging infections?

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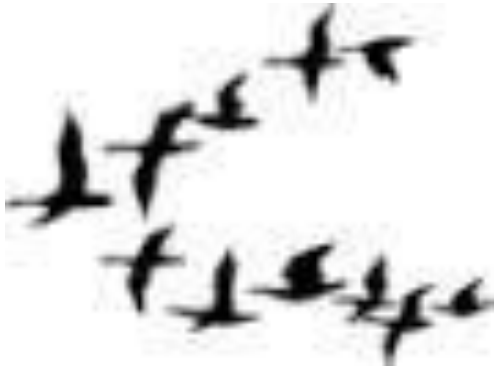
Main objectives

1. Highlight key evidence from the recently completed VIP Trial (Phase IIb trial)
2. Highlight the lessons learned about performing vaccine trials among people who inject drugs and how that might apply to other vaccines (e.g. COVID-19);
3. Highlight the challenges that were experienced and how those were addressed;
4. Compare progress on HCV vaccine development with COVID-19 and the rapid roll-out of vaccines for COVID-19 (perhaps providing a foundation for future progress)?
5. 3-5 key take-home messages.

The VIP Study



- The **Vaccination Is Prevention (VIP) Study** was a placebo-controlled randomized double-blinded trial testing the ***safety, efficacy, and immunogenicity*** of a HCV preventive vaccine among PWID in San Francisco, Baltimore and Albuquerque.
- At enrollment, participants were: aged 18-45 years old, HCV-negative, HIV-negative and reported injecting drugs in the last 90 days.
- Participants were randomized to receive experimental vaccine or placebo, and were followed for up to 29 months for adverse event monitoring, health and immunological outcomes.

VACCINATION IS PREVENTION

VIP

The First Randomized, Double-Blind, Placebo-Controlled Efficacy Trial of vaccines to Prevent Chronic Hepatitis C Virus Infection in an at-Risk Population

- **INTRO:** A safe and effective vaccine to prevent chronic HCV infection is essential to reduce transmission, providing rationale for the first HCV vaccine efficacy trial. We evaluated safety and efficacy of a recombinant chimpanzee adenovirus-3 vector vaccine prime followed by a recombinant modified vaccinia Ankara virus boost, both encoding HCV nonstructural proteins in a Phase I/II randomized, double-blind, placebo-controlled efficacy trial.

METHODS:

- HCV uninfected adults, 18-45 years old and at-risk for HCV infection due to active injection drug use, were randomized to receive the prime-boost regimen or placebo at Days 0 and 56. Sites: Baltimore MD, San Francisco CA, Albuquerque NM
- Randomization was stratified by sex and IL28B genotype
- Participants were monitored for vaccine reactogenicity, adverse events, and HCV viremia.
- Primary outcome: progression to chronic HCV infection at 6 months.
- Secondary outcomes: HCV RNA change from incident infection and peak HCV RNA.

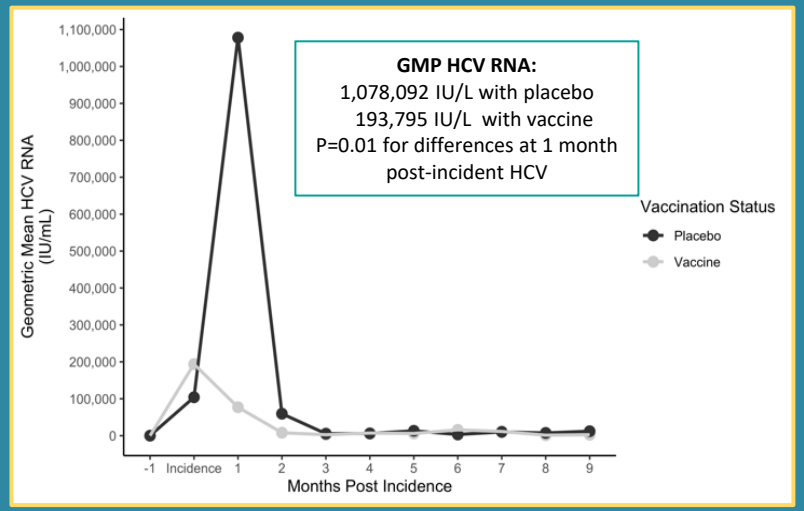
RESULTS:

- 548 people enrolled
- Randomization was even:
  - 78% male; 61% White; 14% Hispanic
  - Median age: 29 (range: 18-45)
  - Mean BMI: 25.37 (sd 5.28)
  - IL28B CC: 41%

A prime-boost HCV vaccine regimen did not provide protection against chronic infection.

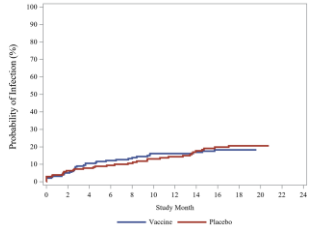
Population	Vaccine		Placebo		Hazard Ratio	95% CI	P-value
	N Censored	N Chronic HCV	N Censored	N Chronic HCV			
ATP	261	14	259	14	1.53	0.66, 3.54	0.32
mITT	256	19	257	16	1.66	0.79, 3.49	0.18

There were significant differences in viral trajectory after infection:

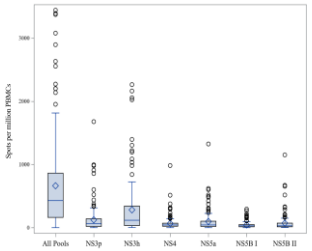


- **Safety** : Solicited adverse event post either dose (vaccine vs. placebo)*: Local:* 75% vs. 36%; *Systemic:* 59% vs. 47%. 79 SAEs were reported for 65 subjects (12%). None related to the vaccine regimen.

- **HCV incidence**. Overall incidence**:** 13.0 infections/100 person-years.



- **Immunogenicity:**
- 78% of vaccine recipients responded to vaccine
- Peak response was 7 days post-MVA (boost) vaccine



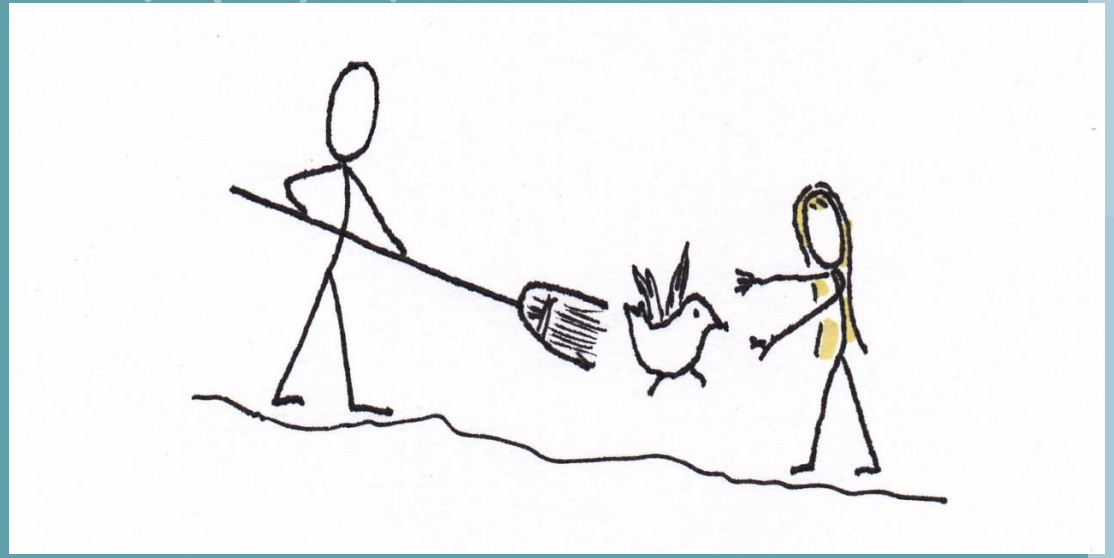
Page K, Melia MT, Veenhuis RT, Massaccesi G, Wagner K, Osburn WO, Giudice L, Stein E, Asher A, Vassilev V, Lin L, Nicosia A, Capone S, Folgori A, Weirzbicki MR, Chang S, Liang J, Ghany M Gorman R, Wolff P, Lum PJ, Cox AL,
NEJM 2021

ClinicalTrials.Gov: NCT01436357

Working With Young adults who inject drugs a marginalized community in a large clinical trial

Or

Herding Birds – The Recruitment and Retention of a Highly Disenfranchised Population



- Caycee K. Cullen[1], Alice K. Asher, RN, Ph.D.[2], Ellen S. Stein, MPH[1], Paula J. Lum, MD, MPH[3], Kimberly Page, PhD, MPH[4]

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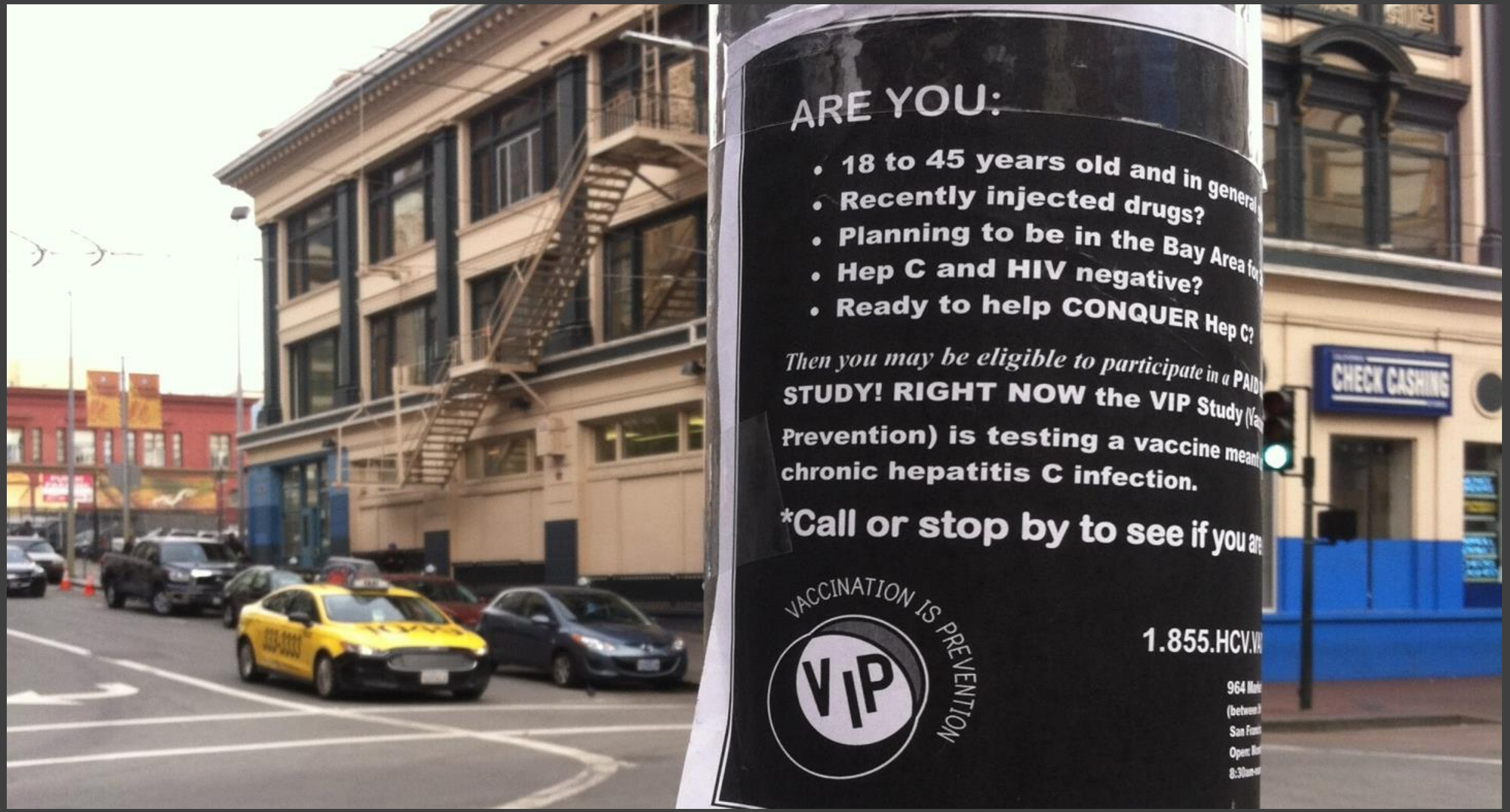
Lessons learned about performing vaccine trials among people who inject drugs and how that might apply to other vaccine trials or implementation (e.g. COVID-19)

- Implementation:
  - *Recruitment:* have a plan, have 2 plans, and probably 3. Be nimble and responsive to the pressures that the population faces (transportation, housing, remuneration, information and mis-information, etc)
  - *Eligibility* – as with any trial it is critical to clearly define eligibility. "Standard" guidelines for 'healthy' may have to be reviewed and revised. Again – being nimble can improve participation. For example: many women may be anemic. Can you safely include them in a trial, and provide them with information and resources for iron supplementation?
  - *Informed consent and enrollment*: being is a trial with an experimental product is a big deal. Be clear about the requirements and challenges people will face. We did include a comprehension assessment after the informed consent process.

Our Plan For Success

- An in-depth outreach plan was developed by seasoned outreach workers to guide recruitment of study population. Recruitment happened on foot, by bike, and mobile screening
- The clinical research sites were located in areas with high numbers of PWID.
- An aggressive retention plan was created to achieve the highest possible retention and minimize possible bias associated with loss-to-follow-up.
- A toll free phone number with 24-hour staffing allows potential participants to screen at any time or call for support/referrals.


ARE YOU:
• 18 to 45 years old and in general
• Recently injected drugs?
• Planning to be in the Bay Area for
• Hep C and HIV negative?
• Ready to help CONQUER Hep C?
Then you may be eligible to participate in a PAID
STUDY! RIGHT NOW the VIP Study (Va
Prevention) is testing a vaccine meant
chronic hepatitis C infection.
*Call or stop by to see if you are
VACCINATION IS PREVENTION
VIP
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8:30am-
CHECK CASHING

The Big Challenges

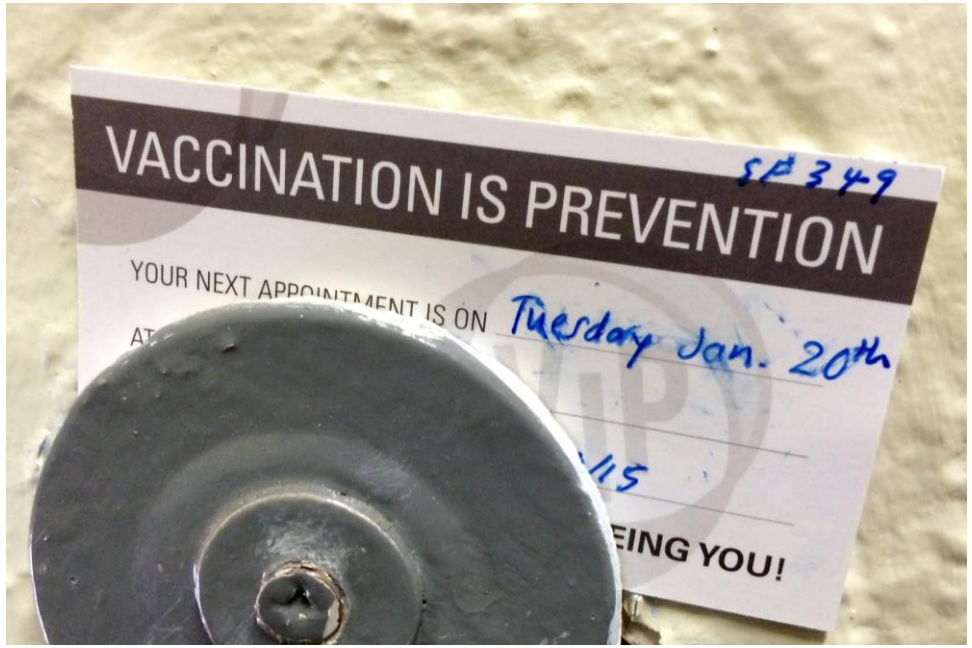
- Loss to follow-up: high rates of incarceration, death, and moving (even though an inclusion criteria included planning to stay in the area for 2 years)
- Missed visits
- Comorbidities: mental health, polydrug use
- One site had more adverse events
  - They were not solicited, but regularly Reported

How We Did It

- **The street -** Outreach workers map routes on foot and bike to identify areas for recruitment and appropriate times for outreach. We established “a presence”.
- **Secondary recruiters -** Enrolled participants are trained to refer people to the study and inform outreach workers of new places to go to maximize recruiting efforts.
- **Education –** VIP staff work with agencies who serve PWID, i.e. syringe service programs (SSP) and community clinics, to provide HCV prevention education trainings for staff and clients that include study aims, goals and eligibility criteria.
- **Collaboration –** Outreach workers draw on pre-existing relationships with staff at homeless drop-ins and street-based health providers for direct referrals.
- **Flyering –**Flyers at SROs, clinics, key street locations, SSPs, alleys, parks, public bathrooms, tents-communities, shelters, bars, and any other places a PWID is likely to be.
- **Cultural competence in the clinic:** All clinic personnel were provided training and education about optimal ways to engage the population; building trust, being available, avoiding judgement

Retention

- **Contact forms** – Obtain detailed contact information is collected including: address, email, phone number, social media, and family contacts.
- **Location -** Participants are seriously queried about where they spend time and services accessed.
- **Photo –** With permission, a face shot is taken.
- **Database –** All information is stored on a secure database. Tracking notes are added to document updated participant information.
- **Reminders –** Participants receive study reminders by street contact, cell phone, email, home visits, text messages and social media.
- **No show –** If a participant misses an appointment, all contact information given is used to make every effort to get that person in. Calls to local jails, hospitals, and the medical examiner's office are made if necessary.
- **Smart phones –** 3 of the 4 VIP staff carry study smart phones and are available to field calls/texts and access the database beyond the work day.



“If history provides any lesson, the elimination of an infectious disease requires both an effective vaccine and a successful vaccination strategy”

Liang et all, NEJM 2021

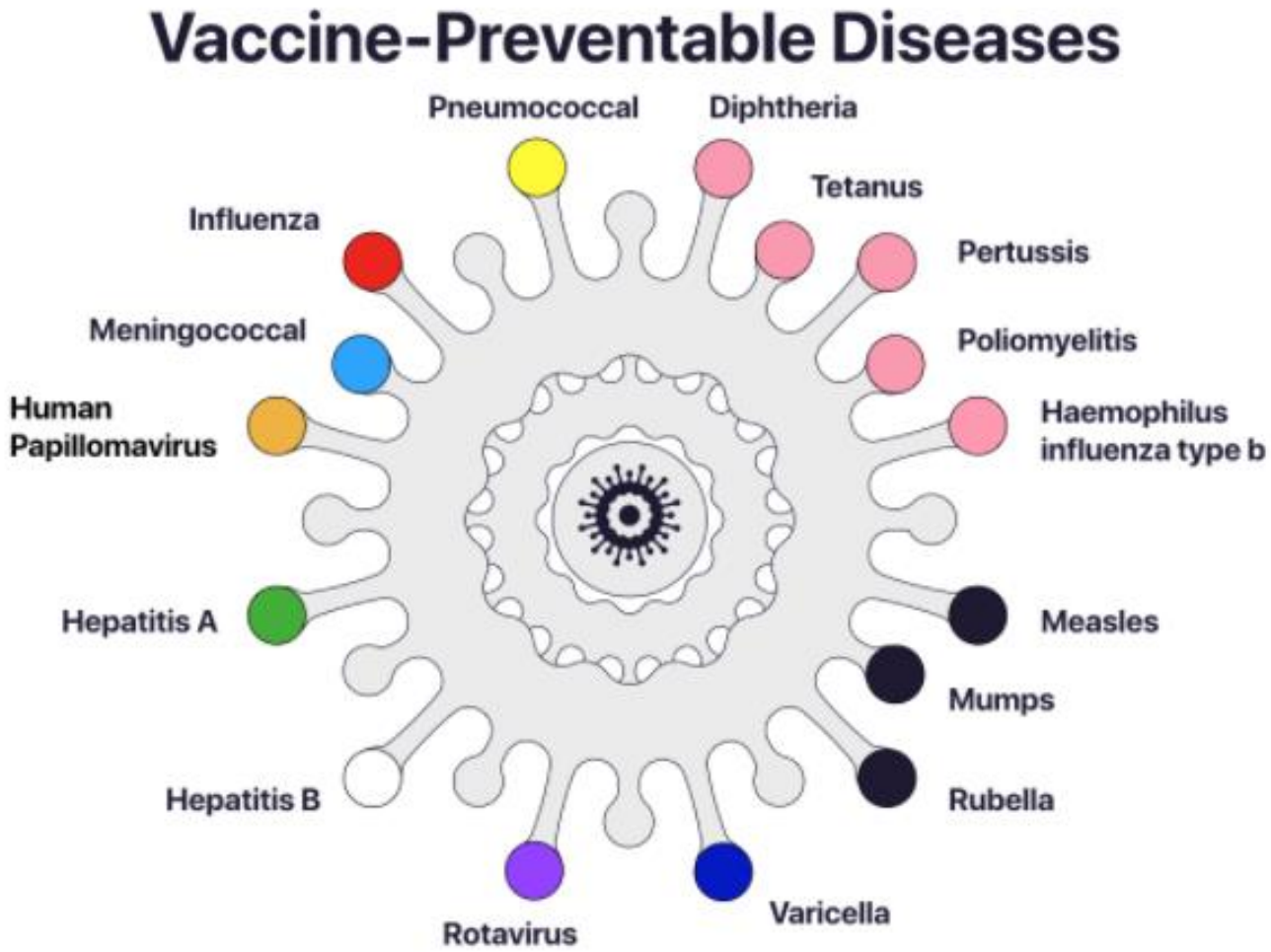


Image from Vaccine Practice for Health Professionals 1st Canadian edition . Ed. St Amant et al., https://ecampusontario.pressbooks.pub/immunizations/part/preface/

Compare progress on HCV vaccine development with COVID-19 and the rapid roll-out of those vaccines

HCV

- Discovery 1989
- Few candidates:[1]
  - Adenovirus vector – efficacy testing in 2012 – 25 years later
  - Others[2]: Recombinant HCV env protein-based, simian adenoviral vector targeting multiple genotypes, virus-like particles
- Barriers:
  - Limitations to HCV culture systems and lack of in-vitro model
  - Limited animal models (chimp [moratorium]; rat [viral structure differences]
  - Viral diversity and rapid mutation
  - Incomplete understanding of protective immune responses
  - Challenges with at-risk populations for testing vaccines; changing to non-clinical sites could improve retention
  - Stigma towards people with high risk

SARS-CoV-2

- Discovery 2019
- Many vaccines were developed, tested, approved and deployed in 2020 - <1 year after identification; Currently 8 approved globally[3]
- WHO: as of 20 October, 126 vaccines in clinical development; 196 in pre-clinical[3].
- Facilitators:
  - Coronavirus vaccines were already in development
  - Using new and existing technologies
- Barriers:
  - Variants may influence efficacy

1. Bailey et al., Gastroenterology 2019
2. Youn et al., J Virol 2008; Elmowalid et al., PNAS 2007; Christiansen et al., SciRep 2018; von Delft et al., Vaccine 2018; Garrone et al., SciTranMed 2011;
3. https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html; 4. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

From COVID-19 vaccine to HCV vaccine

Recent advances in structural and genetic understanding of HCV Env and bnAb responses create new hope for the rational design of HCV vaccine antigens to elicit potent cross-nAbs in vaccination."[1]

- Design and development of Modified mRNA Encoding Core Antigen of Hepatitis C Virus[2]
- HCV E2 core Nanoparticle vaccine2
  - a novel HCV vaccine strategy that combines E2 optimization and nanoparticle display to stimulate robust B cell response upon vaccination
- Optimization of envelope glycoprotein immunogens capable of eliciting a bNAb response. Reviewed by 4

1 Yechezkel et al., Viruses 2021; 2. Sharifnia et al., Iranian Biomedical J 2019; 3. He et al., Science Advances 2020; 4. Fuerst et al., Frontiers Microbio 2020

Some other important considerations

- Some of the COVID-19 vaccines use vectors – to which people will develop immune responses and memory. There may be limitations to using these vectors for other vaccines such as HCV.
  - For example: the J&J COVID-19 vaccine, *aka* Ad26.COV2-S (recombinant), is a recombinant adenoviral vector that contains the sequence that encodes the spike protein (S) of the SARS-CoV-2 virus. Immunity to Ad26 from COVID-19 vaccine could preclude use for HCV.

Some key take-home messages.

- It is an especially opportune time now to take advantage of the interest and innovations happening in vaccine development.

- We need to continue to engage with people and communities at risk of HCV to find ways to better conduct trials and meet the scientific and regulatory requirements for high quality trials.
  - *PWID can be successfully enrolled and and engaged in a demanding clinical trial requiring multiple study visits over a long period of time.*
  - Many participants *reported enjoying frequent contact with VIP staff. Positive feedback included feeling useful and responsible (to VIP Study), being able to demonstrate reliability, and take their research participation seriously.*
- Controlling HCV will require *one or more vaccines* in addition to:
  - large scale screening, treatment of infected people, prevention and harm reduction for persons at risk.

Thank you

- We are indebted to all the participants in our research studies from whom we continue to learn how be equitably address and improve health.
- Thank you to the INHSU Conference organizers and attendees!