

Panel Discussion 1

The MPT Map So Far: Target Product Profiles for Multipurpose RH Vaccines

Without leaps of imagination, or dreaming, we lose the excitement of possibilities. Dreaming, after all, is a form of planning."

--**Gloria Steinem**

Commercially Available Multipurpose Pediatric Vaccines

- Measles, Mumps and Rubella (MMR) vaccine: mixture of three live attenuated viruses. No booster required
- Diphtheria, Tetanus, Pertussis (DTP); available and widely used for 60 years
- Pentavalent (DTaP, IPV, Hib) in Canada for 10 years
- Hexavalent (DTaP, IPV, Hib, HBV) available in some European countries

Acceptability/Access Drivers of Multipurpose Pediatric Vaccines

- Combination pediatric vaccines are often the preferred option when available
- Combination pediatric vaccines improve parental and provider satisfaction and schedule compliance by decreasing the number of injections
- Combination vaccines may decrease pain, be more convenient, improve compliance with on-time immunization, improve record-keeping, and be more cost-effective.

Request for Multipurpose Vaccine Concepts

Table 1. Technical Features of a Multipurpose RH Vaccine

General Technical Vaccine Features	Specific Technical Features of Multipurpose Vaccine Concept
Pathogen Targeted	e.g. HSV/HIV/HPV; chlamydia/gonorrhea; sperm
Immunogen Type	e.g. subunit, live, DNA
Adjuvant	e.g. systemic = MPL; mucosal=VLP
Manufacturing Platform	e.g. synthesis, mammalian, bacteria, yeast, plant
Prime/boost Strategy	e.g. systemic/nasal, nasal/nasal, nasal/cervical
Formulation	e.g. liquid, powder, device, film, nanoparticles

Table 2. Target Product Profile (TPP)

Parameter	Optimally Preferred	Minimally Acceptable	Challenges Addressed with Concept
Indication	e.g. HPV/HBV/HSV/HIV	e.g. HPV/HBV	e.g. long timelines by having successive generations: 5 year (HPV/HBV), 10 year (HPV/HBV/HSV), 15 year (HPV/HBV/HSV/HIV); Access and efficacy limitations of therapies, and other prevention technologies
Target Population	e.g. Women/girls; Developed and developing regions	e.g. Sexually active women, developing regions	e.g. Large global burden for women; high STI prevalence globally
Product Presentation/Delivery Mode	e.g. Nasal powder prime delivered with syringe, cervicovaginal film boost delivered with finger; 90% acceptability	e.g. Prime/boost delivery acceptable to 70% of users	e.g. No injections, no needle disposal, no need potential for needle reuse; safety concerns by public about injected vaccines
User-action Required	e.g. self-administered vaginal boost	e.g. pharmacy administered nasal boost	e.g. acceptability and access with self-administered vaccines
Boost Schedule	e.g. >6 months	e.g. monthly	e.g. Maintaining protective concentrations of cervicovaginal antibodies
Typical Use efficacy	e.g. 90% protected; 100% of individuals have neutralizing concentrations of antibodies in cervicovaginal mucus	e.g. 70% protected; 80% of individuals have neutralizing concentrations of antibodies in cervicovaginal mucus	e.g. poor acceptability of low efficacy
Side effect profile	e.g. Minimal	e.g. Slight irritation or discharge	e.g. Safety concerns about injected vaccines
Additional benefits			e.g. Prevent cervical, anal, rectal, oral, liver cancer
Shelf life	e.g. two years	e.g. one year	e.g. unless vaccines are manufactured in target country, distribution may be more costly
Storage needs	e.g. No cold chain	e.g. refrigerator if container opened	e.g. Cold chain increases costs
Price	e.g. \$1/dose	e.g. \$10/dose	e.g. Large, cost-sensitive market
Infrastructure Required	e.g. Pharmacy for prime	e.g. Clinic	e.g. no cold chain required

Multipurpose RH Vaccine Working Group: Concepts Submitted

- *Laurel Lagenaur; Osel, Inc.
- *Allen Wu; Nanjing University
- *Jiri Mestecky, University of Alabama, Birmingham
- Melissa Herbst-Kralovetz/Hugh Mason, University of Arizona and Arizona State U
- Larry Stanberry, Columbia University
- Robin Shattock, Imperial College
- Ali Harandi, University of Gothenburg
- *Jessica Cohen/Maggie Kilbourne-Brook/Richard Walker/Jeremy Blum, PATH
- Kenneth Palmer, University of Louisville
- Roy Curtiss, Arizona State University
- *Kevin J Whaley, Mapp Biopharmaceutical, Inc.

*Participants in MPT Symposium in DC

Jiri Mestecky; University of Alabama, Birmingham

Parameter	Optimally Preferred
Indication and Mechanism	HIV-1, HPV Stimulation of humoral and cellular immune response
Target Population	Women
Immunogen, Adjuvant, and Delivery Mode	DNA systemic (IM); subunit mucosal (intranasal, sublingual, vaginal), CM cellulose (mucoadhesive)
User-action	Clinic visit for prime; self-administered mucosal boost
Boost Schedule	Systemic DNA prime; mucosal subunit boost 2-3 months after prime, then ~1X/year
Typical Use efficacy	
Side effect profile	None expected
Additional benefits	
Shelf life	
Storage needs	
Price	Mucosal less than systemic
Infrastructure	Clinic

Prime/Boost Strategies and Mucosal Tolerance (Mestecky)

- Mucosal tolerance (systemic unresponsiveness to antigens previously encountered by the mucosal route) has been induced in humans after oral ingestion or intranasal application of antigens, but definitive studies in the female genital tract have not been conducted.
- Does initial application of antigens (priming) through the female genital tract induce the mucosal tolerance, which in its parameters is analogous to that produced by other mucosal routes including the ingestion of intranasal application?
- The answer to this question would immediately focus the immunization strategies in productive and immunologically acceptable direction.
- For additional background and perspective see: Mestecky J, Russell MW, Elson CO. Perspectives on Mucosal Vaccines: Is Mucosal Tolerance a Barrier. *Journal of Immunology* 2007;179:5633-5638

Allen Z Wu; Center for Public Health Research, Nanjing University

Parameter	Optimally Preferred
Indication and Mechanism	HIV-1, HSV-2, HPV Targeted Induction of Broadly Neutralizing Antibodies (Systemic)
Target Population	General Population; Developed and developing regions
Immunogen, Adjuvant, and Delivery Mode	Synthesized and chemically modified peptide; Advax adjuvant; injected liquid
User-action	Visit clinic
Boost Schedule	3-6 Months
Typical Use efficacy	HIV (75%); HSV/HPV (90%); 100% of vaccine recipients develop neutralizing serum antibodies to each pathogen in the peripheral blood
Side effect profile	Minimal
Additional benefits	Reduce 2 nd transmission
Shelf life	12 months
Storage needs	Cold chain
Price	\$2/dose
Infrastructure	Clinic

Lawrence R Stanberry; Columbia University

Parameter	Optimally Preferred
Indication and Mechanism	HSV, HPV, HIV Maintain protective concentrations of cervicovaginal antibodies and/or detectable pathogen specific T-cells
Target Population	Women and post-menarcheal girls; Developed and developing regions
Immunogen, Adjuvant, and Delivery Mode	Intravaginal tampon delivery of a nanoemulsion vaccine containing recombinant HSV-2 glycoprotein D and recombinant HPV 16 and 18 L1 protein and HIV glycoprotein 120
User-action	Self-inserted by the user at bedtime and removed the next morning; 90% acceptability
Boost Schedule	2 and 6 months following priming dose; yearly boost?
Typical Use efficacy	HPV (100%); HSV (70%); HIV (60%); 100% of vaccine recipients develop neutralizing serum antibodies to each pathogen in the peripheral blood
Side effect profile	None
Additional Benefits	
Shelf life	Two years
Storage needs	No cold chain required
Price	\$1/dose
Infrastructure	Pharmacy

Ali Harandi; University of Gothenburg

Parameter	Optimally Preferred
Indication and Mechanism	HSV, HIV Sustained protective levels of antibody and cell-mediated
Target Population	Women and girls in the developed and developing world
Immunogen, Adjuvant, and Delivery Mode	Subunit trimeric gp140 and HSV gD; versatile adjuvant system (PLA-NPs), systemic liquid formulation and mucoadhesive gel carrying both antigens and immunostimulatory molecules to the same dendritic cell (prevents systemic inflammatory responses)
User-action	Single vaccination visit (systemic and mucosal); 90% acceptability
Boost Schedule	3 months following priming dose
Typical Use efficacy	90% protected; 100% of individuals develop sustained protective levels of antibody and cell-mediated response
Side effect profile	None
Additional Benefits	
Shelf life	Two years
Storage needs	No cold chain required
Price	\$5/dose
Infrastructure	

Melissa-Herbst Kralovetz; University of Arizona
Hugh Mason; Arizona State University

Parameter	Optimally Preferred
Indication and Mechanism	HPV, HBV Systemic and mucosal neutralizing antibodies
Target Population	Females and males in developed and developing countries
Immunogen, Adjuvant, and Delivery Mode	VLP subunits, MPL or aloe-derivative adjuvant, nasal prime/boost (systemic prime/nasal boost)
User-action	Pharmacy administered, nasal delivery
Boost Schedule	>1 year
Typical Use efficacy	HPV (95%), HBV (95%)
Side effect profile	Minimal
Additional Benefits	Manufacturing platform is versatile and appropriate for large, cost-sensitive markets.
Shelf life	3 years
Storage needs	No cold chain
Price	< \$1/dose
Infrastructure	Pharmacy

Laurel Lagenaur; Osel Inc.

Parameter	Optimally Preferred
Indication and Mechanism	HSV, HIV, HPV Systemic and mucosal immune responses
Target Population	Women; developed and developing regions
Immunogen, Adjuvant, and Delivery Mode	DNA or subunit prime with HPV VLPs, gD, gp120 (IM); lactococcus cocktail expressing gD, HPV E6/E7, HIV gag for mucosal boost (tablet)
User-action	Self-administered oral tablet of Lactococcus
Boost Schedule	monthly boost?
Typical Use efficacy	HSV (80%); HIV (80%); HPV (>90%) 100% of vaccine recipients develop neutralizing concentrations of antibodies in cervicovaginal mucus
Side effect profile	Minimal
Additional Benefits	Manufacturing platform is versatile and appropriate for large, cost-sensitive markets. Stimulate innate immune response?
Shelf life	6 months
Storage needs	No cold chain required, room temperature
Price	< 0.13 \$/dose
Infrastructure	Clinic or Pharmacy

Roy Curtiss; Arizona State University

Parameter	Optimally Preferred
Indication and Mechanism	HPV, sperm (immunocontraceptive can be provided separately); Antibodies in fallopian tubes and in cervicovaginal mucus plus systemic antibodies and CMI
Target Population	Girls and women where HPV vaccines are not accessible and/or dissatisfied with existing long acting contraceptives
Immunogen, Adjuvant, and Delivery Mode	Salmonella vectored subunits: (a) L1 capsomeres (possibly with L2 peptide), (b) cocktail of sperm antigens; oral tablet
User-action	Oral tablet from pharmacy (or self administered?)
Boost Schedule	X2 for two months followed by yearly boosts
Typical Use efficacy	HPV (100%), sperm (?%)
Side effect profile	Minimal
Additional Benefits	Manufacturing platform is versatile and appropriate for large, cost-sensitive markets.
Shelf life	3 years
Storage needs	Ambient
Price	< \$1/dose
Infrastructure	Clinic or Pharmacy

Robin Shattock; Imperial College

Parameter	Optimally Preferred
Indication and Mechanism	HIV, HSV
Target Population	Women
Immunogen, Adjuvant, and Delivery Mode	Co-delivery of immunogens (trimeric gp140 boosts following DNA prime), and microbicides (1% tenofovir or dapivirine) via an intravaginal ring. Mucosal adjuvant is R848 (a TLR 7/8 agonist) to sustain mucosal memory
User-action	Insert and retain intravaginal ring,
Boost Schedule	Every three months
Typical Use efficacy	Potential for enhanced efficacy
Side effect profile	Minimal
Additional Benefits	
Shelf life	
Storage needs	
Price	
Infrastructure	

Kenneth Palmer, University of Louisville

Parameter	Optimally Preferred
Indication and Mechanism	Dual purpose HPV (multiple types) vaccine plus griffithsin microbicide (HIV, HSV)
Target Population	Sexually active women and girls in developing and developed populations
Immunogen, Adjuvant, and Delivery Mode	L2 epitope fusion with griffithsin (immunogen/adjuvant); intravaginal ring (or PVA film) for burst release of HPV vaccine (L2-griffithsin fusion protein) and sustained release of griffithsin as a microbicide
User-action	Self-insertion of vaginal ring (or film)
Boost Schedule	Systemic prime boosted with nasal/vaginal or sublingual/vaginal; boost monthly for up to 1 year
Typical Use efficacy	
Side effect profile	Minimal
Additional Benefits	Manufacturing platform is versatile and appropriate for multi-boost, multi-target, cost-sensitive markets.
Shelf life	2 years
Storage needs	No cold chain
Price	\$1/dose
Infrastructure	Pharmacy

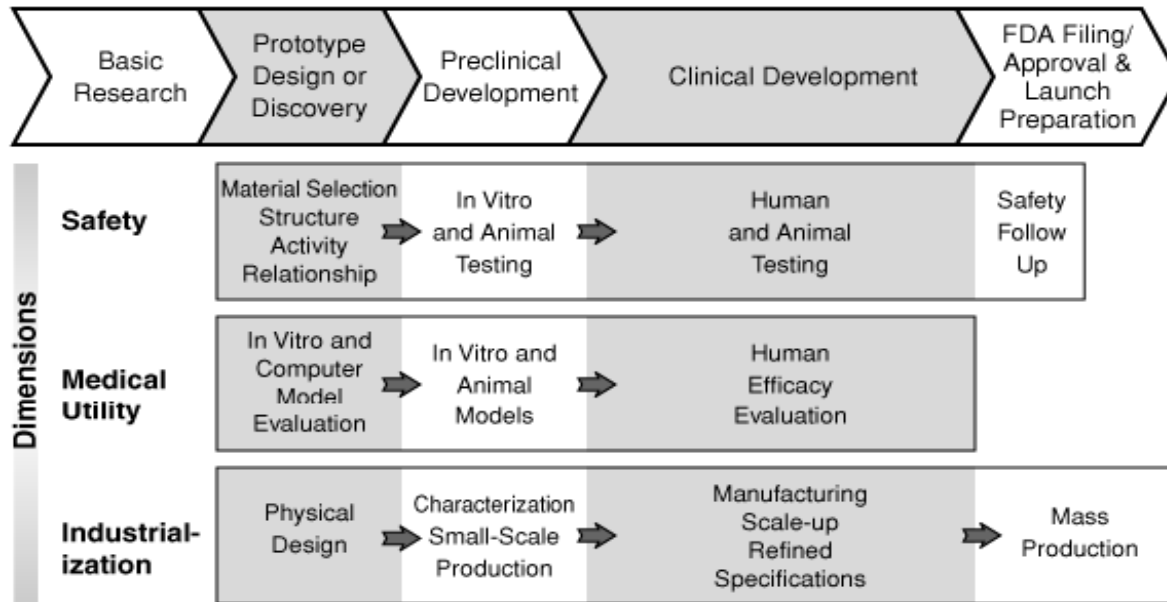
Kevin J Whaley; Mapp Biopharmaceutical, Inc.

Parameter	Optimally Preferred
Indication and Mechanism	HSV, HIV Systemic and mucosal protective concentrations of neutralizing antibodies
Target Population	Women/girls; Developed and developing regions
Immunogen, Adjuvant, and Delivery Mode	gD/Fc fusion protein, gp41 anti-idiotypic; nasal prime delivered with dry inhaler; cervicovaginal boost delivered as film; FcRn-mediated transport across epithelium
User-action	Self-administered cervicovaginal boost
Boost Schedule	1 and 2 months following priming dose; monthly/yearly boost?
Typical Use efficacy	HSV (90%); HIV (90%); 100% of vaccine recipients develop neutralizing concentrations of antibodies in cervicovaginal mucus
Side effect profile	Minimal
Additional Benefits	Manufacturing platform is versatile, rapid and appropriate for multi-boost, multi-target, cost-sensitive markets
Shelf life	Two years
Storage needs	No cold chain required
Price	\$1/dose
Infrastructure	Pharmacy

Consensus Target Product Profile

Parameter	Optimally Preferred
Indication and Mechanism	HSV, HIV, HPV Systemic and mucosal protective concentrations of neutralizing antibodies (and cell mediated immunity)
Target Population	Women/girls; Developed and developing regions
Immunogen, Adjuvant, and Delivery Mode	Well-characterized immunogens (but range of adjuvants and delivery modes)
User-action	Pharmacy or self-administered boosts
Boost Schedule	Mucosal boost schedule uncertain
Typical Use efficacy	HSV (70-90%); HIV (70-90%); HPV (>95%)
Side effect profile	Minimal
Additional Benefits	Important
Shelf life	Years
Storage needs	No cold chain required
Price	\$1/dose
Infrastructure	Pharmacy

Critical Path for HSV/HIV/HPV Vaccines



	Prototype	Preclinical Development	Clinical Development	Approved
Safety		Mucosal HSV, HIV, HPV	Systemic HSV, HIV	Systemic HPV
Efficacy		Mucosal HSV, HIV, HPV	Systemic HSV/HIV	Systemic HPV
Industrialization		Mucosal HSV, HIV, HPV	Systemic HSV/HIV	Systemic HPV

Aspirational Timelines for Advanced Clinical Trials

Proposed Concept	< 5 years	< 10years	< 15years	< 20 years
Generation 1	Mucosal tolerance and boosting strategies in female genital tract	Systemic HSV/HPV/HIV (Mucosal HIV/HSV/HPV)		
Generation 2			Mucosal HIV/HSV/HPV	
Generation 3				Viral/bacterial multipurpose RH vaccine

Comments

- Multipurpose RH vaccines are technically feasible
- Multipurpose RH vaccines are a goal (based on historical preference by end-users and providers), however the map and the timing for the development of multipurpose vaccines remains to be determined.
- Although each STI vaccine could be developed separately, the IMPT is attempting to determine when it is appropriate (e.g. efficiencies in time, money, acceptability, global health) to initiate combination studies in parallel.