Addressing the “Science to Service” Gap Through Implementation Science: What Success Looks Like

Nicolette Naidoo: Technical Head Research: Implementation Science, Wits RHI

01.06.2018

12th Interest Workshop 2018
Kigali, Rwanda
Disclosure Statement

Nothing to disclose
Presentation outline

- What is Implementation Science?
- Why does Implementation Science matter?
- What kind of questions can Implementation Science answer and methods used?
- Examples of success and considerations for new technologies and programming
  - What success looks like – Differential Success in the Roll out of the HPV vaccine
  - Looking ahead - New Technologies for HIV Prevention

HIV Self Screening  PrEP for Key Populations
“We know what we have to do, but we don’t know how to do it”

(Ridde, 2016)
What exactly is it?

“The study of methods and strategies to promote the uptake of interventions that have proven effective into routine practice, ...examines what works, for whom and under what circumstances, and how interventions can be adapted and scaled up in ways that are accessible and equitable.”

- Global Alliance for Chronic Diseases

Implementation science begins where efficacy trials leave off

- Pierre Barker
Successful implementation in its simplest form requires that the research evidence is strong, the context receptive to change, and the change supported by appropriate facilitation.
Stages of Implementation Science:

Incorporating the 3 legs of IS

1. **GENERATING KNOWLEDGE** - To determine what works and how it can work at scale
   - Research Question
   - Research Design and Protocol Development
   - Building Local Capacity through Participatory Approach to the Protocol Development
   - Formative Research
   - Research Study Implementation and Outcomes

2. **MANAGING KNOWLEDGE** - What are the best ways (platforms/messages) to reach a range of stakeholders
   - Results Dissemination and Utilisation (Policy)

3. **USING KNOWLEDGE** - How can evidence be integrated into programs?
   - Landscape Mapping to Examine the Contextual Factors and Adapt
   - Demand Creation – Identifying Effective Messaging to Generate Demand for the Intervention
   - Identifying the Challenges and Facilitating Factors
Why does Implementation Science matter?

- Promising research but unrealised application and potential (public health benefit) in real world settings
- Allows us to understand the challenges associated with taking interventions to scale
  - Context
  - Understanding factors associated with delivery and uptake of intervention – path dependence
  - Demand Creation (market segmentation)
  - Who to engage to ensure sustainability i.e. clinicians, policy makers, and community
- Health care and outcomes are inequitable

However, from development to scale – a complex interplay of a multitude of factors can delay scale
In the past, diffusion-dissemination strategies have resulted in about 14% use of evidence-based programs after about 17 years.

Benefits of accelerated scale; however can only be achieved through rapid learning and understanding of what impedes or facilitates programme implementation.

**Implementation Science Outcomes and Methods?**

**IMPLEMENTATION OUTCOMES**
- Acceptability
- Adoption
- Appropriateness
- Costs
- Feasibility
- Fidelity
- Penetration
- Sustainability

**SERVICE OUTCOMES**
- Efficiency
- Safety
- Effectiveness
- Equity
- Patient-Centeredness
- Timeliness

*IOM Standards of Care

**PATIENT OUTCOMES**
- Morbidity
- Mortality
- Health Status
- Quality of Life

- Case studies
- Qualitative research
- Process evaluation to identify implementation factors (measure of intervention/implementation fidelity)
- Quality Improvement
- Participatory Action Research
- **Pragmatic trials**
  - Cluster randomization
  - Hybrid
  - Stepped Wedge Trials
  - Before/after designs with interrupted time series

*Source: Bryan Weiner, 2014 – FHI360 symposium on Implementation Science*
A case study on HPV vaccine introduction

These cancers are caused by Human Papillomavirus

Every 2 minutes, a woman dies from cervical cancer.
## Cancer cases attributable to HPV worldwide

(Population Attributable Fraction)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Population Attributable Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer</td>
<td>100%</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>88%</td>
</tr>
<tr>
<td>Vaginal cancer</td>
<td>78%</td>
</tr>
<tr>
<td>Penile cancer</td>
<td>50%</td>
</tr>
<tr>
<td>Oropharyngeal cancer</td>
<td>31%</td>
</tr>
<tr>
<td>Vulval cancer</td>
<td>25%</td>
</tr>
</tbody>
</table>

De Martel et al., *IJC*, 2017
Incidence of HPV related cancers - much higher in less developed countries

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>No: of cases</th>
<th>No: attributable to HPV</th>
<th>No: and % attributable to HPV by development status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Less developed</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>530 000</td>
<td>530 000</td>
<td>450 000</td>
</tr>
<tr>
<td>Vulva</td>
<td>27 000</td>
<td>12 000</td>
<td>4 100</td>
</tr>
<tr>
<td>Anus</td>
<td>27 000</td>
<td>24 000</td>
<td>12 000</td>
</tr>
<tr>
<td>Penis</td>
<td>22 000</td>
<td>11 000</td>
<td>7 600</td>
</tr>
<tr>
<td>Vagina</td>
<td>13 000</td>
<td>9 000</td>
<td>5 700</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>85 000</td>
<td>22 000</td>
<td>6 400</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>700 000</strong></td>
<td><strong>610 000</strong></td>
<td><strong>490 000</strong></td>
</tr>
</tbody>
</table>

Three highly effective safe HPV vaccines

<table>
<thead>
<tr>
<th>THREE VACCINES ARE LICENSED AND APPROVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervarix® (bivalent): prevents precancerous lesions from HPV types 16 and 18</td>
</tr>
<tr>
<td>Gardasil® (quadrivalent): prevents precancerous lesions from HPV types 16 and 18 and anogenital warts from HPV types 6 and 11</td>
</tr>
<tr>
<td>Gardasil® 9 (nonavalent): prevents lesions from types 6, 11, 16, 18 plus types 31, 33, 45, 52, 58.</td>
</tr>
</tbody>
</table>
Cervical cancer incidence vs HPV vaccine coverage
However, access and coverage in low and middle income countries (L/MIC) remained low.
Disproportionate burden of cervical cancer experienced by developing countries and HPV vaccine coverage, 2014

GAVI ALLIANCE TACKLES CERVICAL CANCER
EVERY YEAR, 266,000 WOMEN DIE OF CERVICAL CANCER. OVER 85% OF THOSE DEATHS ARE IN DEVELOPING COUNTRIES

Global HPV vaccine programme introduction 2014-2018

What makes this good Implementation Science?

WHAT SHALL BE IMPLEMENTED?

HOW WILL IT BE IMPLEMENTED?

WHO SHALL DO THE WORK OF IMPLEMENTATION?
**Trajectory of HPV discovery to vaccine approval**

*(The ‘What’ of Implementation Science)*

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1920</td>
<td>Pap smear introduced into clinics for cervical cancer screening</td>
</tr>
<tr>
<td>1940</td>
<td>George Papanicolaou develops the “Pap smear”</td>
</tr>
<tr>
<td>1970</td>
<td>Richard Shope’s studies of CRPV and warts in rabbits provided the first mammalian model of cancer caused by a virus</td>
</tr>
<tr>
<td>1980</td>
<td>HPV DNA and virus particles (Koilocytic atypia) found in abnormal cervical smears</td>
</tr>
<tr>
<td>1990</td>
<td>Active HPV genes (E6/E7) identified and transforming properties described</td>
</tr>
<tr>
<td>2000</td>
<td>A HPV16 VLP vaccine tested in humans demonstrates safety and high immunogenicity</td>
</tr>
<tr>
<td>2010</td>
<td>FDA approves HPV vaccines for young women and subsequently boys</td>
</tr>
<tr>
<td>2014</td>
<td>Rwanda starts to prepare for national HPV rollout</td>
</tr>
</tbody>
</table>

- IARC declares HPV6 and HPV11 as group 1 carcinogens (e.g., oncogenic) for cancers of the cervix.
- Phase III studies of 2- and 4-valent HPV L1-VLP vaccines show high safety, immunogenicity, and efficacy against vaccine-related HPV types.
- FDA approves the use of an HPV test as a primary screening procedure prompting re-evaluation of clinical algorithms.
- Approval of 9-valent L1 VLP vaccine.

**Note:**

- HPV therapeutic vaccine trial using overlapping HPV16 E6/E7 peptides induces a T-cell response and associated lesion regression in VIN patients.
- Oral HPV infection strongly associated with oropharyngeal cancer.
- Imiquimod used to treat VIN patients.

© 2015 American Association for Cancer Research
Incidence rates of cervical cancer in Rwanda and East Africa

Source: Human Papillomavirus and Related Diseases Report, Rwanda. HPV information centre 2017
Leadership and defiance in the face of scepticism; In April 2009 First Lady Jeanette Kagame met with Merck to initiate advocacy a public private partnership.

On April 26, 2011 Rwanda became the first country in Africa to initiate a national HPV vaccine programme.

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Round 1</th>
<th>Round 2</th>
<th>Round 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls vaccinated in school, no.</td>
<td>91752</td>
<td>89704</td>
<td>88927</td>
</tr>
<tr>
<td>Girls vaccinated outside school, no.</td>
<td>2136</td>
<td>3066</td>
<td>3180</td>
</tr>
<tr>
<td>Total no. of girls vaccinated</td>
<td>93888</td>
<td>92770</td>
<td>92107</td>
</tr>
<tr>
<td>Cumulative coverage (%)</td>
<td>95.04</td>
<td>93.90</td>
<td>93.23</td>
</tr>
</tbody>
</table>

Source: Binagwaho et al. (2012)
STAKEHOLDER ENGAGEMENT
- Multi-sectoral approach (Ministry of Education, Gender and Family Promotion and the Centre for Treatment and Research on AIDS, TB, Malaria and Other Epidemics)
- Health Care Workers
- Technical Working Groups

SUPPLY CHAIN MANAGEMENT AND PLANNING
- Effective distribution system to transport vaccines to 436 health centres
- Cold Chain Management through micro-planning - how much vaccine to procure, storage space and money required, number of vehicles to mobilise and where to send them

SITUATIONAL ANALYSIS
- In-depth Interviews and FGDs to determine KAB pertaining to HPV vaccination
- Misconception re target group – parents wanted to immunise all children; teachers wanted to be vaccinated

EFFECTIVE NATIONWIDE SENSITISATION CAMPAIGN – VACCINE SAFETY AND EFFICACY
- Print Media (newspaper articles, magazines, radio, television)

CAPACITY DEVELOPMENT
- Nurses
- 45 000 Community Health Workers
- Teachers
Determining the most effective delivery platforms (target and delivery strategy)

- 98% of Rwandan girls attend primary school

**Delivery Strategies:**
- School Grade Based Strategy - 3 doses with highest coverage
- Community based strategy to trace and link those absent on vaccination day

- Multi-phased vaccination strategy spanning 3 years

- Involving gatekeepers - Parents were encouraged to accompany learner on day of vaccination
New HIV Infection trends among adults (15+ years), by country, 2010-2016, and 75% reduction targets

- Expanded access to ART has led to declines in AIDS-related mortality
- Number of people living with HIV continues to increase
- New HIV infections have declined but not abated
- Strategies to prevent new infections are needed

Source: UNAIDS, 2013

UNAIDS, HIV Prevention 2020 Roadmap
PrEP
PrEP – not only public health benefit but a health systems strengthening intervention?

- **Achieving HIV prevention targets**
  - International and National Targets (90-90-90, UNAIDS 3 Zeros, NSP)
  - HIV prevention method with high potential to reach women and adolescent girls, who are experiencing disproportionate and growing HIV rates.

- **Implementing combination prevention**
  - Provides additional choice and empowerment for those who do not use other prevention methods.

- **Promoting equity for AGYW, MSM and SW**

- **Building on existing and future health care investments**
  - PrEP delivery can build on other investments to improve health system capacity and coordination.
  - PrEP may be cost effective when delivered to the appropriate sub-segments of target populations by making incremental investments in existing delivery channels.
  - Lay the groundwork for future female-controlled HIV prevention methods.
In many ways, launch is like rocket science. Hundreds of activities all need to happen at predefined moments to a certain standard. As uninspiring as it may sound as a starting point for excellence, organizations first need to ensure that nothing falls between the cracks.

– Hemant Ahlawat, McKinsey & Company
# What’s Needed to Introduce PrEP

Using the value chain to identify what’s needed for introducing PrEP

## Value Chain for PrEP

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PLANNING &amp; BUDGETING</strong></td>
<td>Plan developed to implement WHO PrEP guidelines for targeted populations</td>
</tr>
<tr>
<td><strong>SUPPLY CHAIN MANAGEMENT</strong></td>
<td>PrEP produced, purchased, and distributed in sufficient quantity to meet projected demand</td>
</tr>
<tr>
<td><strong>PREP DELIVERY PLATFORMS</strong></td>
<td>PrEP services delivered by appropriate channels with access to target populations</td>
</tr>
<tr>
<td><strong>INDIVIDUAL UPTAKE</strong></td>
<td>Target populations seek and are able to access PrEP and begin use</td>
</tr>
<tr>
<td><strong>EFFECTIVE USE &amp; MONITORING</strong></td>
<td>Target population adheres to PrEP at recommended frequency and for ideal time period</td>
</tr>
</tbody>
</table>
# Populations and Research Questions for Scaling PrEP

## Key Indicators

### Adolescent girls and young women (AGYW)

- **Prevalence**: 1<br>  - Age 15-19: 5.6%<sup>1</sup><br>  - Age 20-24: 17.4%<br>  - Age 20-34: 31.6%

- **Incidence**: 1<br>  - Age 15-24: 2.54%<sup>1</sup><br>  - Age 20-34 Black African: 4.54%<sup>2</sup>

- Experience higher frequency of participation in transactional sex and high rates of age-disparate relationships

### Men who have sex with men (MSM)

- **Prevalence**: 13-49%<sup>3</sup>
- **Incidence**: 9.5%<sup>3</sup>
- Highest prevalence found in KwaZulu-Natal, Mpumalanga, Gauteng, and Western Cape
- Urban MSM at highest risk
- Over 90% have tested at least once, ~50% in the last month
- HIV programming for MSM as well as high-risk behavior have increased in recent years

### Sex workers (SW)

- **Size**: ~153,000<br>  - **Prevalence**: ~60%<sup>4</sup>
- **Incidence**: Unknown
- High concentration in large and medium urban areas
- **Mining areas and trucking routes** show increased FSW-to-adult female ratios
- Sex work is estimated to contribute as much as 20% of new HIV infections in South Africa each year<sup>5</sup>

## Questions

- What sub-segments of the AGYW are at highest-risk of HIV / highest priority for PrEP?
- How can existing channels be leveraged to deliver PrEP to AGYW?
  - What new channels could be activated to reach AGYW (e.g., SRH, schools)?
- How can South Africa effectively activate channels already reaching MSM to deliver PrEP?
- What service delivery platforms are most effective in providing PrEP to the SW population?
- How will civil society and health providers address structural stigma to ensure reliable and effective access to PrEP for these populations?
- Will initial launch of PrEP in these populations stigmatize use of PrEP for other populations?

## Sources

3. MSM estimates: NDoH, SANAC and UCSF, [http://globalhealthsciences.ucsf.edu/sites/default/files/content/gsi/msm-triangulation-south-africa.pdf](http://globalhealthsciences.ucsf.edu/sites/default/files/content/gsi/msm-triangulation-south-africa.pdf)
KEY QUESTIONS FOR PREP ROLL-OUT

**PLANNING & BUDGETING**

- For which segments of the adolescent girl and young women population (AGYW) and sero-discordant couple populations will it be cost-effective and/or most impactful to deliver PrEP?
- What are the incremental costs of PrEP delivery?
- What sources of funding will be available for PrEP specifically relative to UTT, etc.? What are the Gates Foundation’s Bridge to Scale plans?

**SUPPLY CHAIN MANAGEMENT**

- What lower-cost alternatives could be available for PrEP? When? Will they use the same packaging as the treatment meds (like Truvada), or will they be branded and packaged differently?
- To what extent and when can approval for the population under 18 and/or pregnant women be expected?
- How will PrEP be integrated into existing procurement and distribution mechanisms?

**PREP DELIVERY PLATFORMS**

- To what extent do existing channels reach target populations? What new channels will be needed (e.g., for AGYW)?
- How will healthcare worker engagement be planned for and delivered?

**INDIVIDUAL UPTAKE**

- How might initial roll-out plans (e.g., to sex workers) stigmatize PrEP for other populations?
- How will stigma and community buy-in be addressed for PrEP?
- What are the most effective demand generation strategies to reach target populations?

**EFFECTIVE USE & MONITORING**

- What will be considered “effective use” for each population and how will it be encouraged?
- To what extent will ongoing testing needs for PrEP users further strain health care capacity?
- How will ongoing monitoring be managed?
So... where are we now with PrEP introduction in South Africa?

National roll out to FSWs, MSM and students at Universities and TVETS

Estimated Number of Current PrEP Users: 8,500 – 9,500

Aggregated Target Number of PrEP Users from All Projects – 31,000 (will surpass PEPFAR COP 2018 target of 18,826)

Plans underway to increase access to AGYW through Youth Zones and National Demo Projects

Capacity Building and Demand Creation:

- Implementation pack
- IEC materials using Human Centred Design
- Training
- Social Mobilisation
Globally, disproportionate progress...

Progress toward 90-90-90 Targets

Gap to reaching first 90: 7.5 Million people

Achieved 90% Target

Up from 66% in 2015

Global Status 2016

Australia
Belarus
Denmark
Ecuador
Malaysia
Sweden
Thailand

Austria
Botswana
Cuba
Fiji
Germany
Hungary
Ireland
Italy
Lithuania
Luxemburg
Netherlands
Nicaragua
Rwanda
Romania
South Africa
United Kingdom

Almost there! 85-89%

Who are the 30% undiagnosed PLHIV?
- Key populations
- Men
- Young people

UNAIDS Special analysis, 2017.

Slide courtesy: Bekker, IAS March 2018
And men remain largely under tested
HIV Self Screening (Testing)

- HIVST is a “screening test” or Test for Triage
- HIVST could play a substantial role in accelerating progress towards this goal of 90-90-90.

However in 2015, the barriers to HIVST in South Africa were notable i.e.:

- No indication from the SA DOH that ST is acceptable
- No guidance in place from WHO
- No validated HIVST products available
- Requirements for WHO Pre-Qualification for ST not defined
- Undefined IVD regulatory landscape
- Minimal implementation research
Although acceptability was high, what are the questions that remain and what methods can we adopt to answer them?

Facility-based HIV self-testing for outpatients dramatically increases HIV testing in Malawi: a cluster randomized trial

Frackson Nuka Shaba, Malawi
### Selection of Testing Candidate

- Accomplished through International and National Stakeholder Engagement and Consultation
- WHO prequalification for HIVST devices
- WHO normative guidance on HIVST
- Enabling Environment through Policy Development, Review and Implementation

### Market Research and Demand Creation

- Conduct targeted market research and execute end-user demand creation strategies
- User testing (formative, participatory approaches)
- User segmentation
- Behavioural Economics

### HIVST Delivery Platforms – Demo Projects

- NDoH implementing innovative distribution models
- Strong existing channels for MSM and FSW
- Demo projects can inform plan for AGYW
- Conduct prelim distribution to generate country specific data that strengthens public health rationale and selection of optimal distribution channels
- Where to begin HIV ST? (Know your epidemic)
- How to reach men? (Workplace, transportation hubs, ANC secondary testing)

### Scale Up & Individual Uptake

- Upcoming UTT investments could also enable HIVSS roll-out
- Strong uptake expected in MSM and SW
- Scale up effective HIVST based on country needs
- What is the acceptability among populations?
- Linkage to care
- What is the impact of integrating with other services (example PrEP)?

### Effective Use, Monitoring and Costing

- Conduct targeted assessment of the effectiveness and impact of HIVST distribution models including opportunities for integration within Health Systems
- Conduct costing analysis and modelling to evaluate CE of HIVST approaches at a country level
- What are the costs associated with delivering HIVST?
- Who will pay for supply of Kits?
- Public-Private Partnerships?

---

Adapted from OPTIONS Value Chain Analysis
In summary

“Without implementation research, we are at best, committing valuable resources in the hope that things will work out”

FOCUSED IMPLEMENTATION
SCIENCE CAN BE A CATALYST TO SCALING INTERVENTIONS BY:

- Supporting planning - Understanding dynamic stakeholders’ attitudes and information needs thereby ensuring sustainability (Political Will)
- Refinement/segmentation of target population(s) to reach those most at risk (PrEP landscape analysis, micro planning, behavioural economics);
- Creating awareness and demand through novel participatory approaches (Human Centred Design)
- Understanding which are the most effective channels of delivery, and scenarios of programme organisation that could yield highest gains (integration, combination prevention) - HSTAR
Acknowledgements

Interest Workshop Organising and Scientific Committee

Wits RHI – The Wits Reproductive Health and HIV Institute

- Prof Helen Rees
- Dr Saiqa Mullick
- Mohammed Majam – STAR Initiative
- Diantha Pillay
- Elmari Briedenhann

OPTIONS Consortium