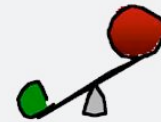




Developing diagnostics for resource-limited settings

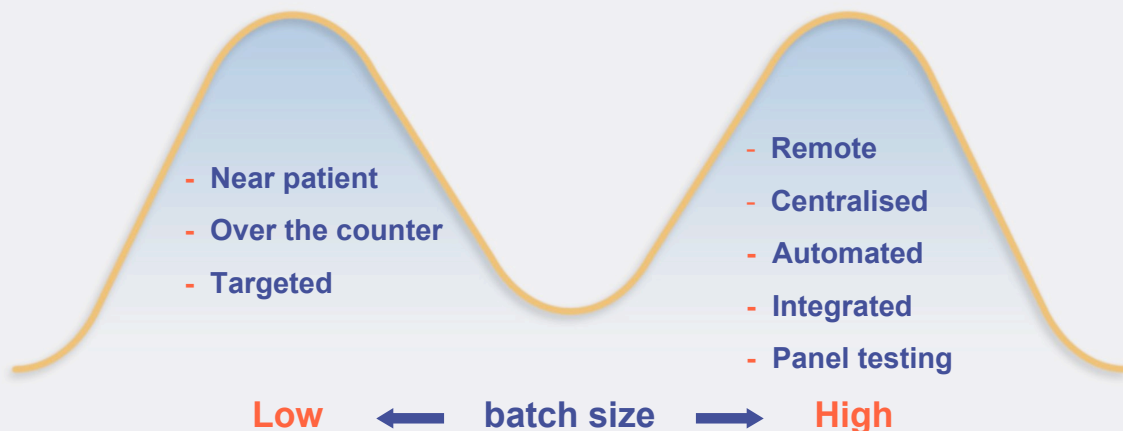
Helen Lee

University of Cambridge



Trends in diagnostics: becoming a bimodal distribution

- Primary health clinics
- Emergency rooms
- Home
- Hospital labs
- Clinical labs



Prevalence of blood-borne viruses in 1,294 donors (Kumasi, Ghana)

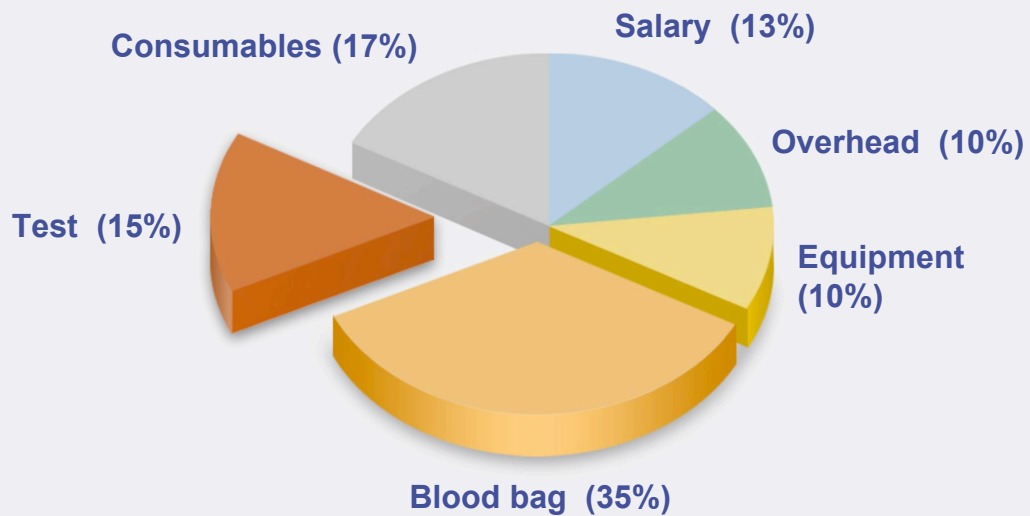
<i>Virus</i>	<i>No. infected</i>	<i>% infected</i>
HBV	204	15.8
HCV	31	2.4
HIV	19	1.5
Total	254	19.6%

Allain et al. 2004

Prevalence of viral markers in blood donors

Country	Prevalence (%)			Cumulative %
	HBV	HCV	HIV	
Botswana	5	10.0	1.0	16
Cameroon	10.7	4.8	7.9	23
Egypt	5	12.0	1.0	18
Malawi	8	1.0	11.0	20
S. Africa	4	0.5	4.5	9
UK (2003)	0.00073	0.00086	0.00074	0.0023

Budget of blood bank at Kumasi, Ghana



Annual budget \$70,000 (7,800 donors)

Opare-Sem 2002

Imbalance of resources

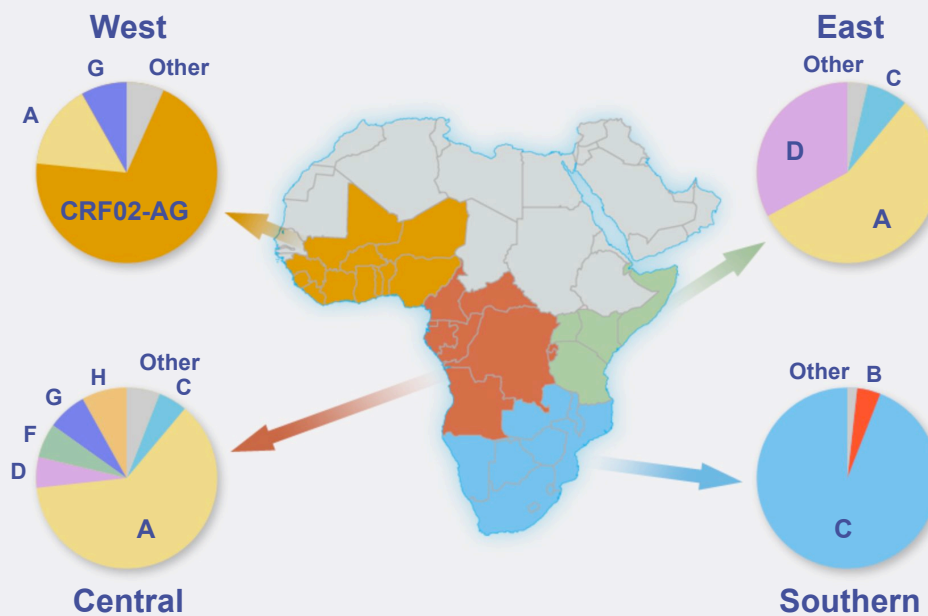


Bias of current test components for viral subtypes

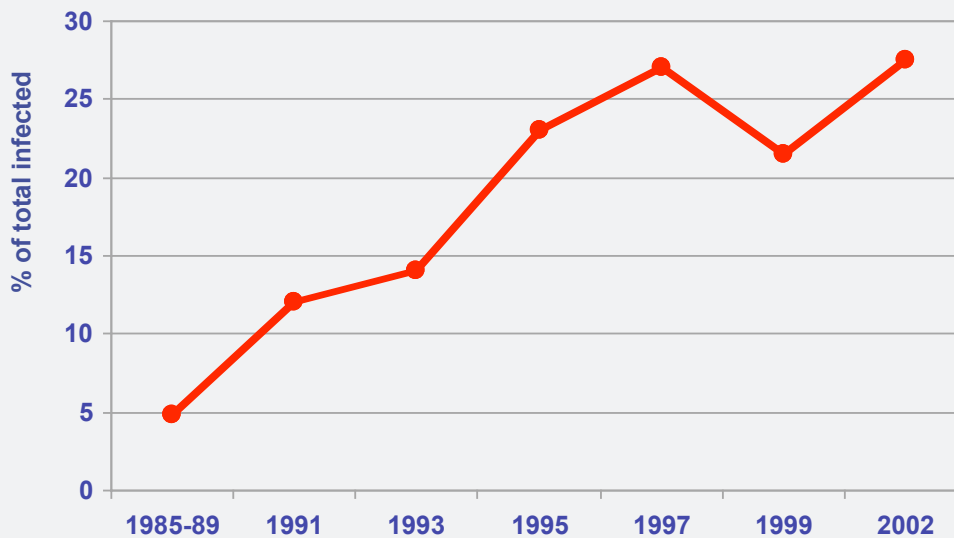
Virus	Subtype	Frequency
HCV	1a	< 5%
HIV	B	< 5%
HBV	A	< 2%

- Test components optimal for developed world
- Insufficient sensitivity for certain geographic areas

HIV-1 subtype distribution in sub-Saharan Africa



Non-B HIV-1 subtype in French blood donors



Diagnostics for resource-limited settings An unmet need

Academia

- Lack of product development expertise
 - Validation
 - Scale-up
 - Documentation
 - Patent protection
- Applied research not valued by environment
- Not their *raison d'être*

Diagnosics for resource-limited settings An unmet need

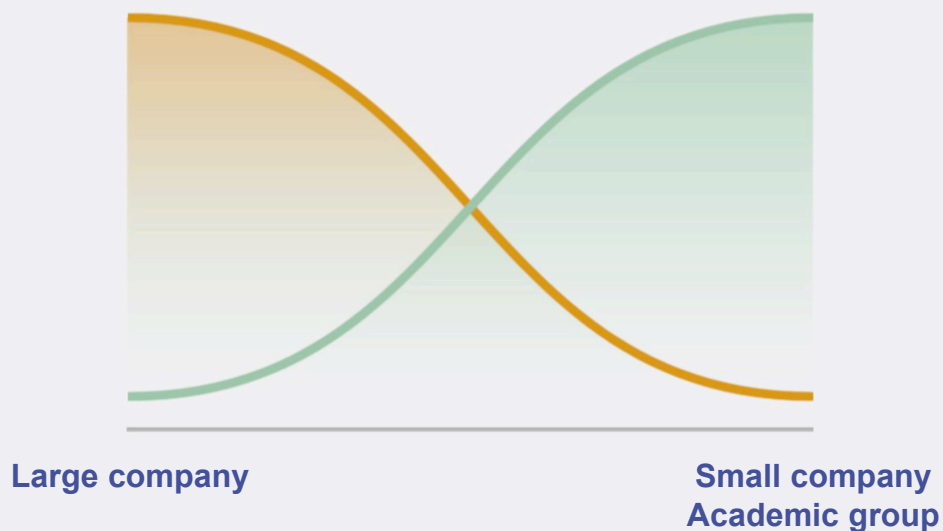
Private Sector

- Low return of investment
- Low profit margin for rapid tests
- Imperative to use existing production line
- Technical inadequacies (stability, sensitivity)
- Problematic marketing/distribution channel
- Difficulties in service, repair and technical support

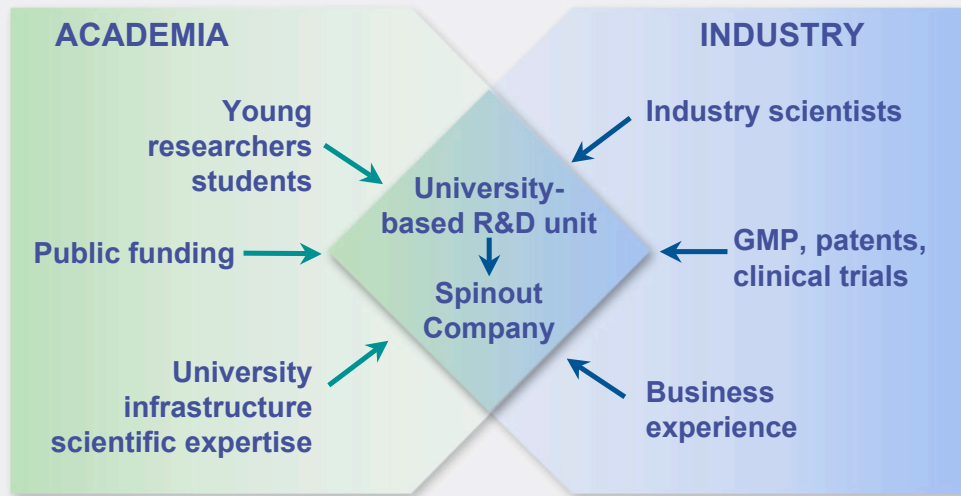
R & D for neglected diseases

Skill & infrastructure

Incentives



Creating a structure that blurs traditional boundaries

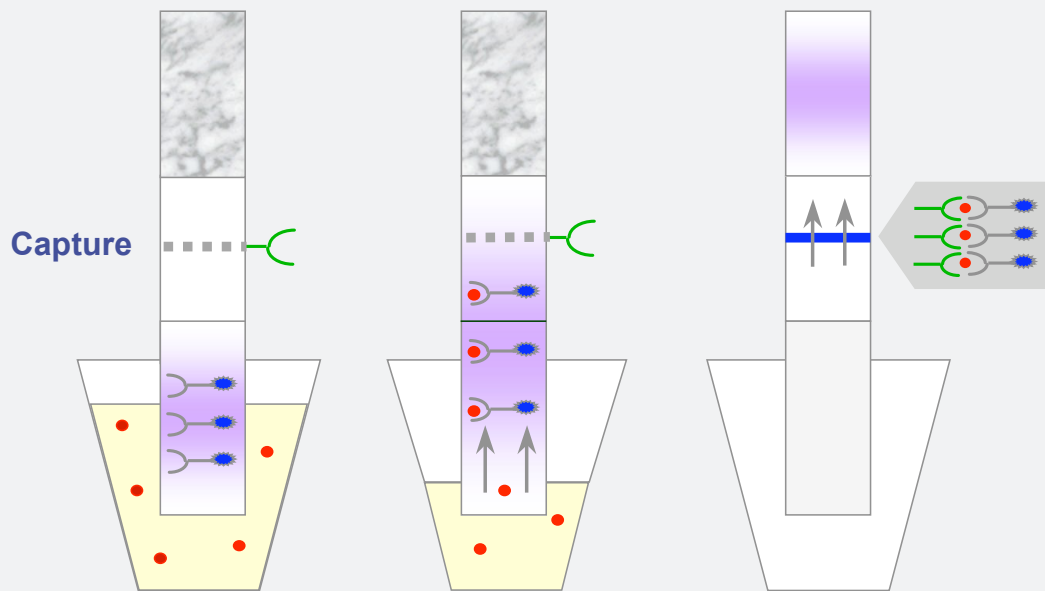


Goal - developing appropriate diagnostics for resource-poor settings

Assay format for developing countries

- Inexpensive, rapid and easy to use
- Stable for high humidity and poor storage/transport conditions
- Use of non-invasive sample types
- Flexible format to meet regional needs
- Designed for simplicity and large volume
- Incorporate cutting-edge technologies

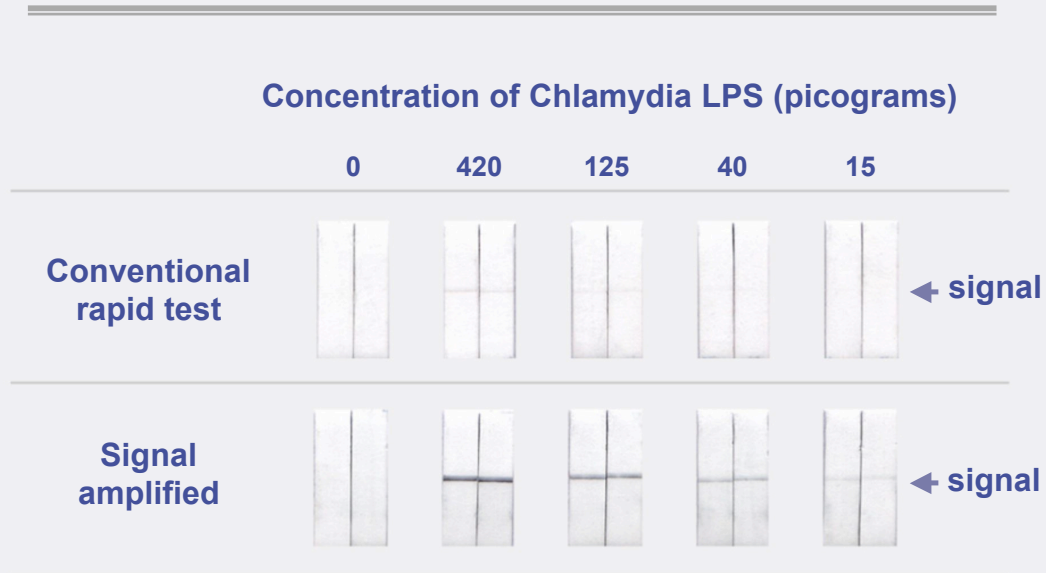
How a dipstick assay works



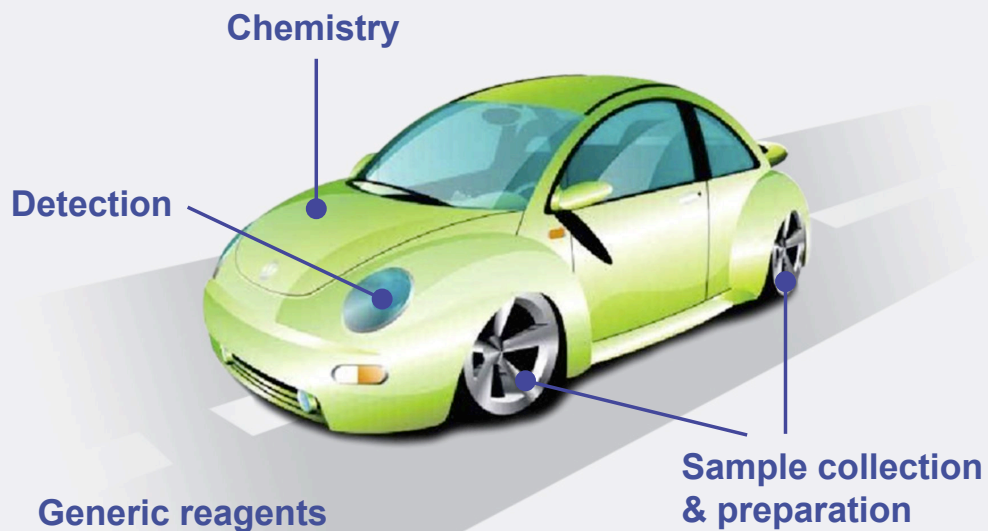
Choosing the first target: *Chlamydia trachomatis*

- 90 million new cases worldwide
- Major cause of infertility and PID
- \$4 billion in US, £100 million in UK
- Cost-effective treatment
- High % asymptomatic infections
- Lack of diagnostic screening tools

Signal amplification technology to improve sensitivity



Components of a diagnostic test



FirstBurst™ - First void urine collector



- Unique collection & disposable device
- Reliable and convenient collection of first catch urine
- Sample with higher bacterial load
- '2003 Best Diagnostic Medical Futures Innovation' award

Chlamydia Rapid Test

Home use

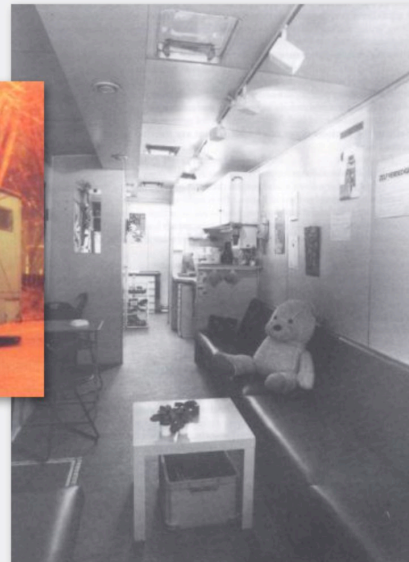


Clinical laboratory use

Field trial in Iloilo, Philippines



The 'Living room' project, Amsterdam

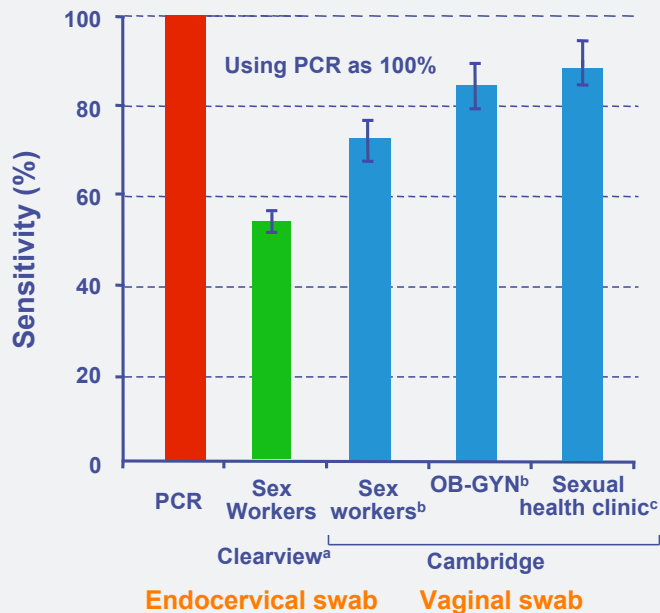


Field trial at Brook, Birmingham



- 98% of study participants found the instructions easy to understand
- 85% of women and 67% of men willing to wait 1 hour or more for their result

Preliminary results of Cambridge *Chlamydia* Rapid Test in vaginal swabs

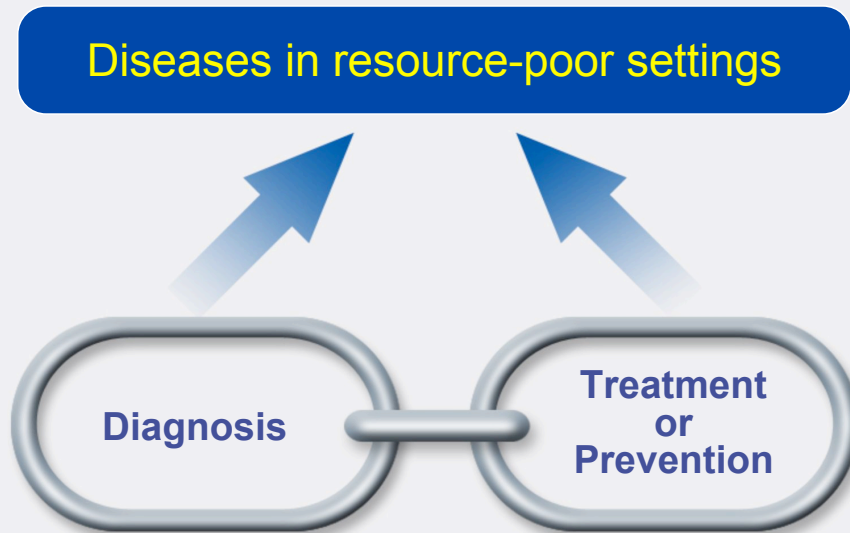


^a Clearview test performed in a high prevalence (sex workers) population in the Philippines

^b Cambridge test performed in a high prevalence (sex workers) population and a low prevalence (OB-GYN) population in the Philippines

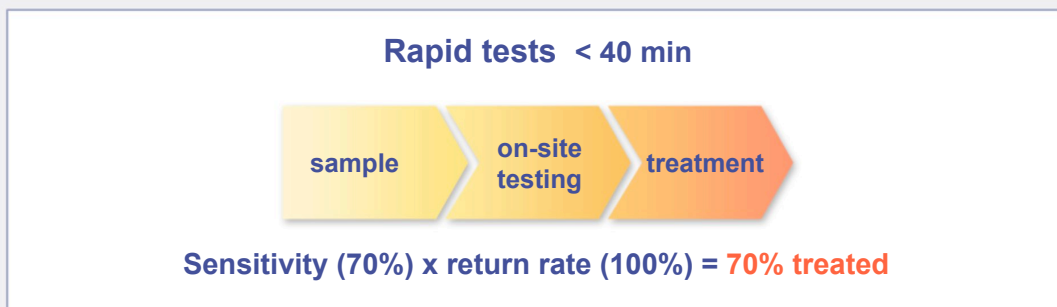
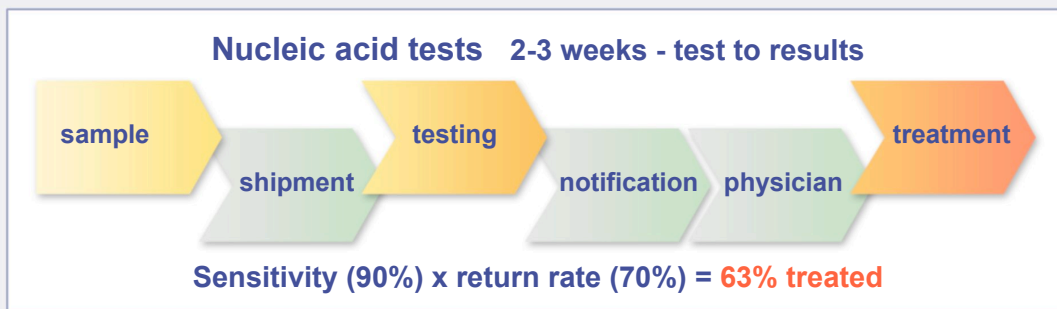
^c Cambridge test performed in a young people's sexual health clinic (16-25) in the United Kingdom

Diagnostics: only part of the equation

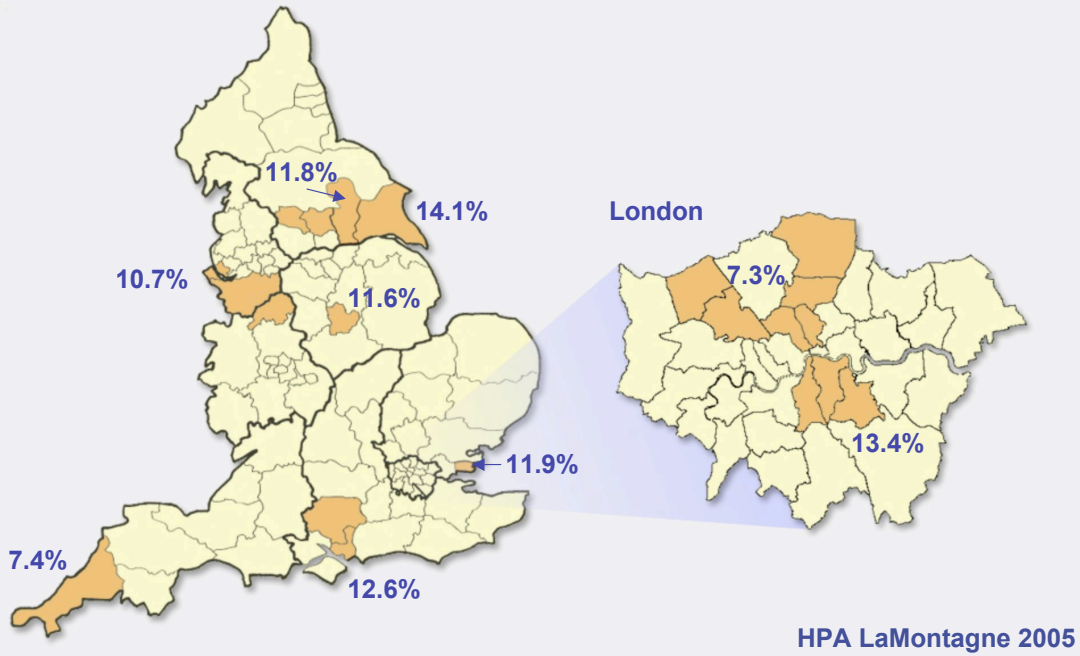


The rapid test paradox

A less sensitive test results in more patients treated

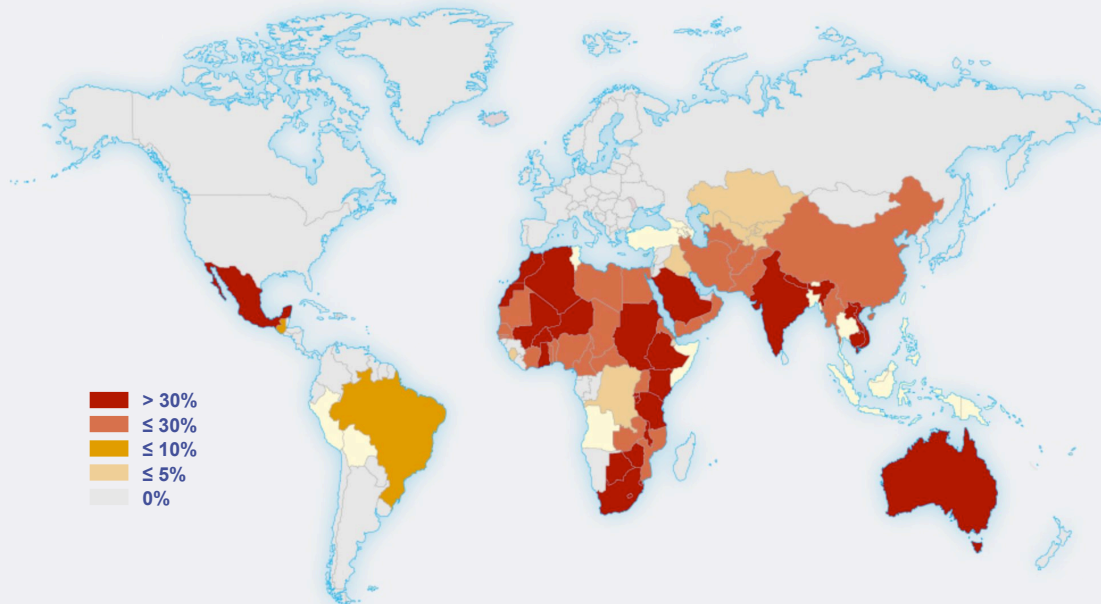


Chlamydia prevalence in UK women 16-24 years old, 2003/04



Blinding Trachoma

- 146 million infected, 3 million blind or visually disabled



Chlamydia Rapid Test performance in eye swabs



Cambridge rapid test

	+	-	Total
PCR	+	49	59
	-	3	205
Total	52	212	264

Sensitivity 83%

Specificity 98.5%

Inadequacy of clinical signs in Trachoma



PCR+ without clinical symptom 35.9%

PCR - with clinical symptom 19.8%

	Rapid test	Clinical signs
Sensitivity	83%	64.1%
Specificity	98.5%	80.2%

Power of nucleic acid testing (NAT)

- High degree of analytical sensitivity
- Specific detection of infectious agent genome
- Applications
 - Early detection during window period
 - Diagnosis of infections in newborns from infected mothers
 - Anti-retroviral therapy monitoring
 - Improvement of the safety of blood supply

Complexity of current nucleic acid test (NAT)

Sample prep



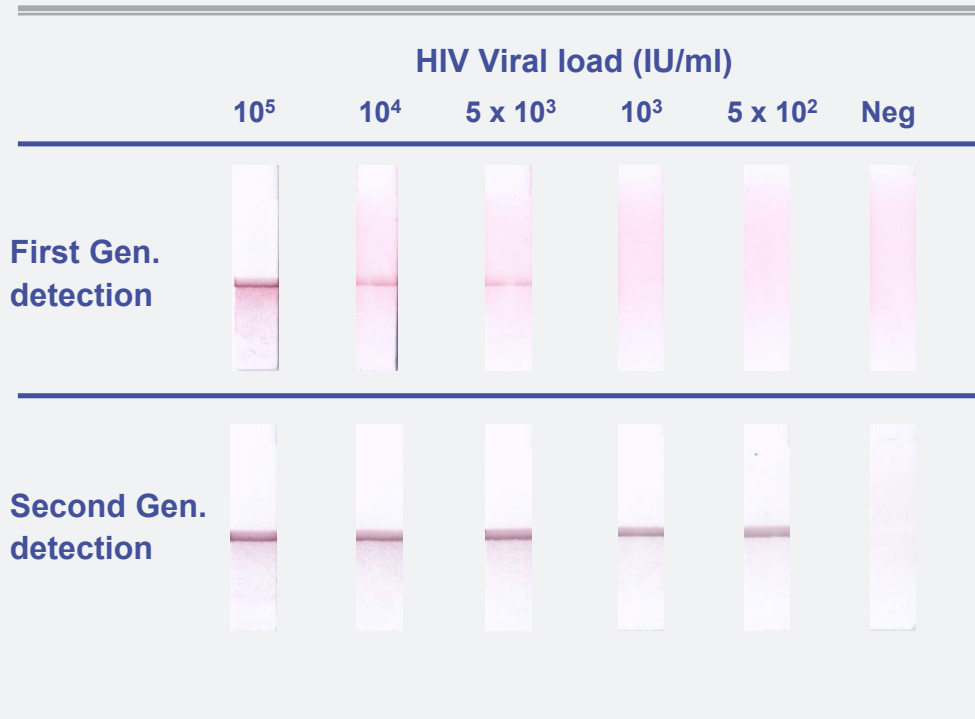
Amplification



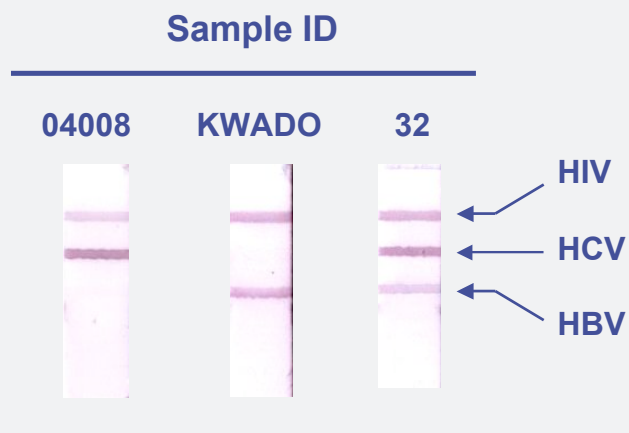
Detection



Visual detection of nucleic acid



Triplex dipstick detection of co-infected clinical samples from Africa

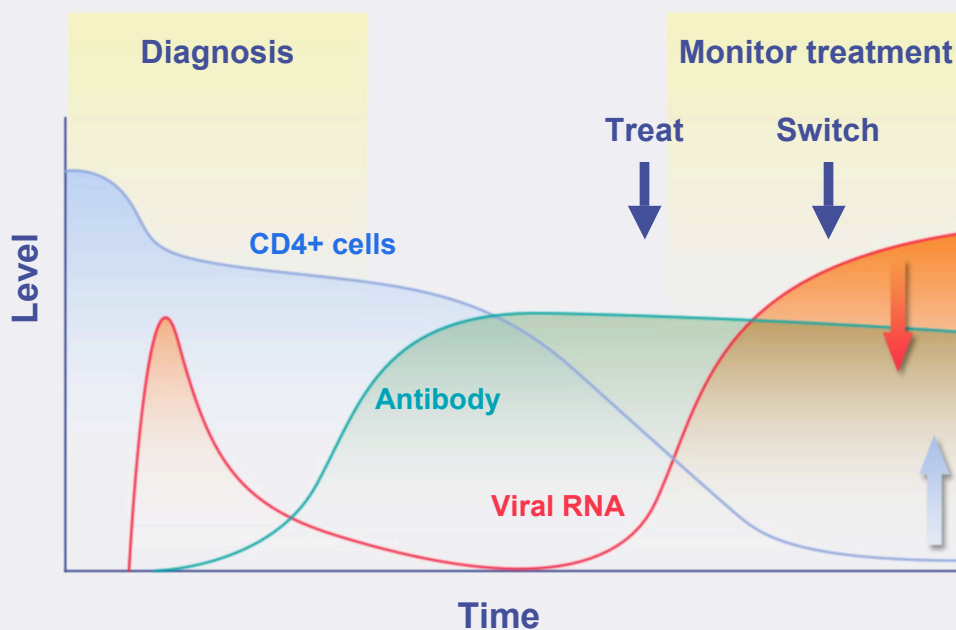


Comparison of TaqMan vs dipstick detection of HIV, HCV & HBV in 303 African samples

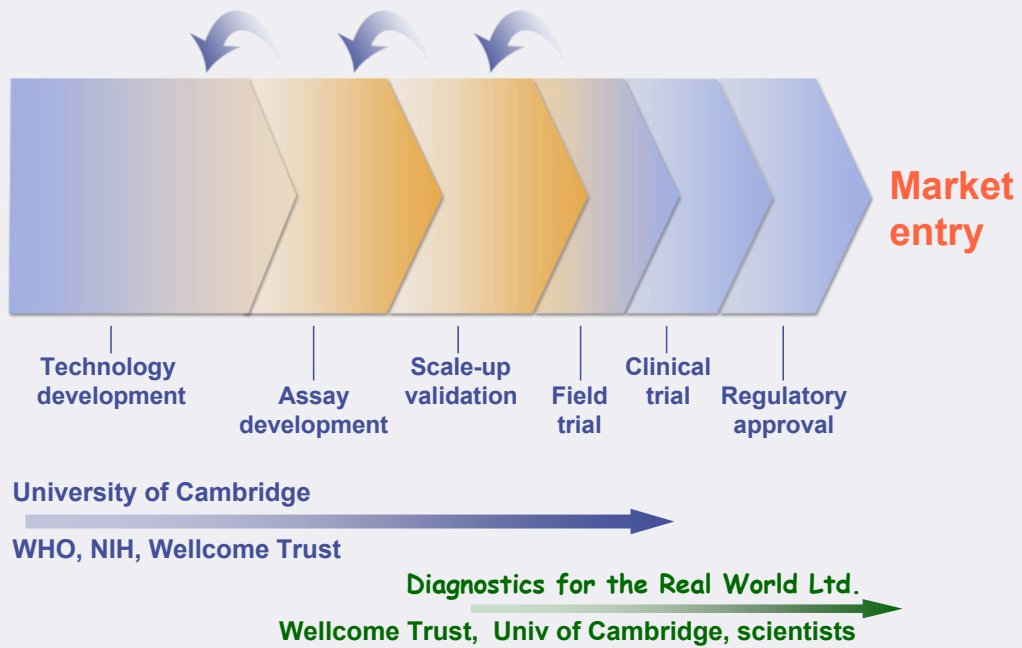
SENSITIVITY	No.	Range (IU/ml)	TaqMan Q-PCR (%)	Dipstick (%)
HIV	36	$2 \times 10^2 - 2 \times 10^6$	97.2	97.2
HCV	34	$3 \times 10^2 - 2 \times 10^7$	100	100
HBV	32	$2 \times 10^1 - 5 \times 10^8$	96.9	96.9
SPECIFICITY	201 negatives		98.5%	100%

Dineva et al. 2005

Evolution of HIV infection



Long cycle of product development



Diagnostics for the Real World Ltd Sunnyvale California

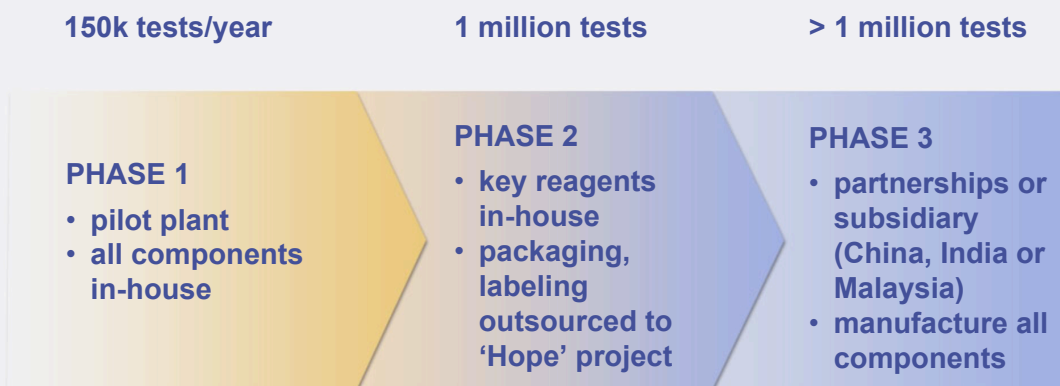


Chlamydia Rapid Test

280 documents for manufacturing and QC



How we will manufacture the products?



- Clinical trials
- Marketing
- Early sales

Continuum of process development and scale-up

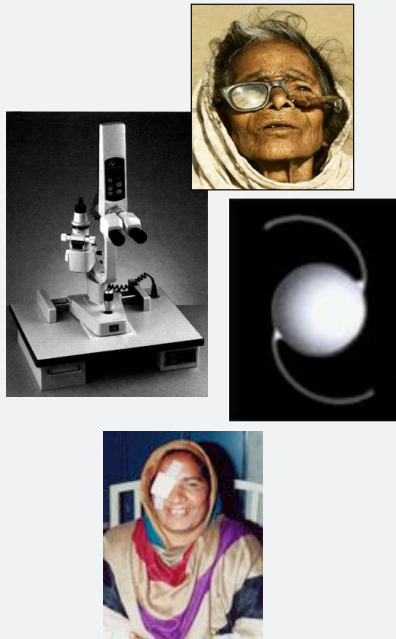
Commercialisation

- **Product differentiation by technical innovation**
- **Good manufacturing process (GMP)**
- **Apply for FDA & EU license**
- **2-tier pricing**
 - 'Cost plus' in developing countries
 - High margin in developed countries
- **Sales via selected distributors or bulk purchase**

What are the challenges?

- **Retain trained personnel**
- **Distribution and commercialisation**
 - corruption
 - perception in developing countries
 - licensing is not the route
- **Funding to develop additional tests**
 - venture is not the route
- **Sustainability**
 - charity is not the route

Technology development & transfer by Fred Hollows Foundation



- 23 million blind worldwide due to cataract
- Modern cataract surgery too expensive and technically complex for developing countries
- Developed robust, compact, portable operating microscope
- Built intra-ocular lens manufacturing sites in Eritrea and Nepal
- Manufacturing output of 520,000 lens/yr at 3.5% of cost
- Export to > 50 countries
- Broad based skill training programmes

Restored sight to 1,000,000 people

2006 Goal: test & treat 1 million women for *Chlamydia*



Resolving trade-offs along the way

Academia	vs	Company
Social responsibility	vs	Profitability
Public health	vs	Private wealth
Control	vs	Cash injection
Business	vs	Idealism

Creating and maintaining a balance between
doing well and doing good

