

# Next generation tuberculosis diagnostics: test and treat

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# Outline

- Needs for test and treat strategy in the context of global TB epidemic
- Xpert MTB/RIF roll out and lesson learnt
- What's new about Xpert MTB/RIF Ultra
- Xpert MTB/RIF Ultra test performance
- E-DETECT TB project
- Conclusions and next steps



# The Global TB epidemic

**10.4 MILLION\***  
estimated TB cases

125,000  
MDR-TB cases  
diagnosed

**6.3 MILLION**  
new cases diagnosed

**MDR-TB**

490000  
estimated new  
cases

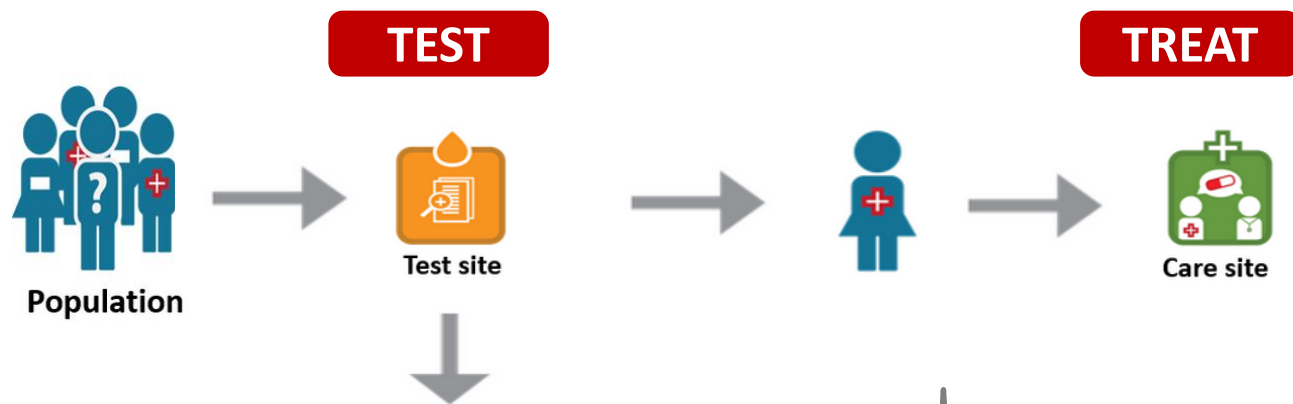
- 10.4 million TB cases
- 1.8 million TB deaths
- 4.3 million undiagnosed
- Up to 30% of cases diagnosed never get treated

## Facts:

- 600 000 with MDR/RR-TB
- Only 22% of MDR-TB cases were enrolled for appropriate treatment



# Test and Treat by Molecular Diagnostics



New generation of Molecular diagnostics  
Should be able to provide diagnosis of TB and  
DR-TB

REFERENCE CENTER

DISTRICT HOSPITAL

MICROSCOPY CENTER

HEALTH POST

COMMUNITY HEALTH WORKER

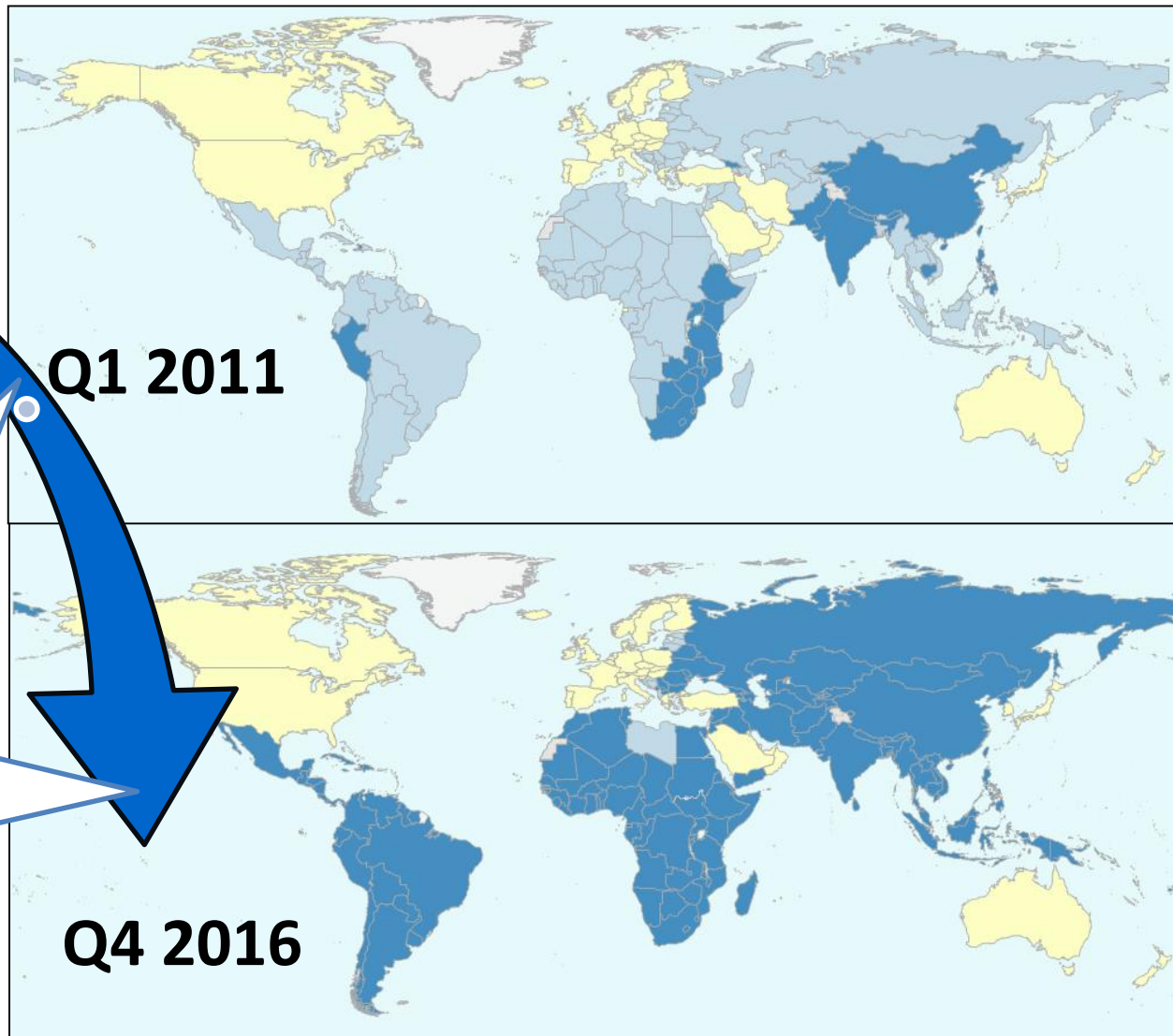


# Xpert MTB/RIF roll-out: global progress



**99** GeneXperts  
(524 modules)  
in the public sector  
in **23** countries

**6,659** GeneXperts  
(29,865 modules)  
in the public sector  
in **130** countries

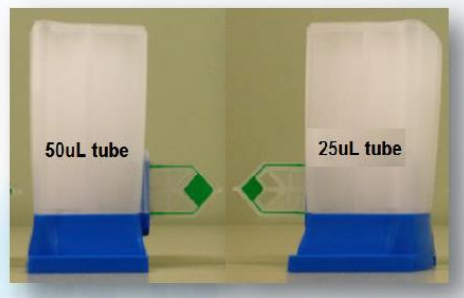


23.1 million Xpert tests have been procured in 130 countries

# Xpert MTB/RIF Ultra: Increased sensitivity for TB detection



- Xpert MTB/RIF Ultra: Detects MTB by targeting **two different multi-copy genes** (*IS6110* & *IS1081*)
- Bigger tube: **double amount of DNA** delivered to PCR reaction



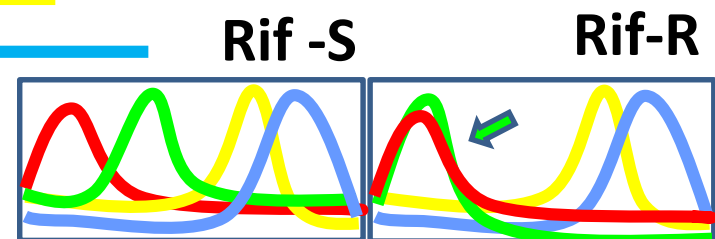
- Fully nested amplification
- More rapid thermal cycling
- PCR cycling optimized to improve sensitivity and specificity
- Semi-quantitative test: Depending on the Ct value of the MTB target, result is displayed as: High, Medium, Low, Very Low, **Trace**

	full ultra	ultra neg	Xpert
Elapsed Time	1:17:00	1:04:53	1:40:58
Ultra time savings vs. G4	0:23:58	0:36:05	

- Melting temperature based analysis to improve RIF resistance detection

5'- GCACCAGCCAGCTGAGCCAATTCATGGACCAGAAACAACCCGCTGTCGGGGTTGACCCACAAGCGCCGACTGTCGGCGCTG - 3'  
 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 525 526 527 528 529 530 531 532 533  
 3'- CGTGGTCGGTCGACTCGGTAAAGTAACTGGTCTTGTGGGCGACAGCCCCAACTGGGTGTTTCGCGGCTGACAGCCGCGAC - 5'

A clear change in T<sub>m</sub> distinguishes wild type from resistant mutant





# Xpert MTB/RIF Ultra: operational characteristics

## Limit of detection (LOD) for *M. tuberculosis* H37Rv

- ~8-fold improvement over the Xpert MTB/RIF assay
- 48% of the samples tested still positive at 2.5 CFU/ml

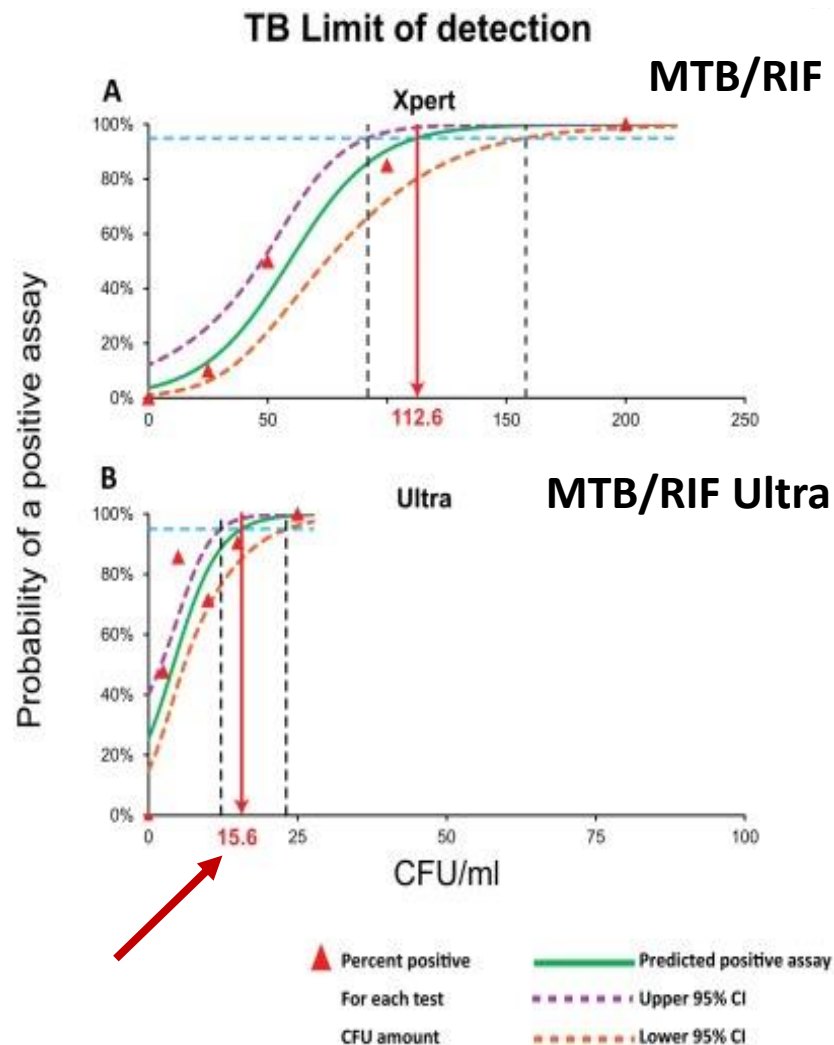
## RIF susceptibility detection comparable between the Xpert MTB/RIF Ultra and Xpert MTB/RIF

## Detection of mutations associated with RIF resistance and silent mutations

- Improved detection of mutants at codon 533
- Differentiate silent mutations at codons 513 and 514

## Better capacity to detect heteroresistance (mutation dependent)

## Highly specific (negative for NTM, Gram pos/neg bacteria)





# Performance of Xpert MTB/RIF Ultra on pulmonary samples



## Comparative accuracy for detection of TB and rifampicin resistance

	Tuberculosis detection*					Detection of rifampicin resistance†	
	Sensitivity: all culture-positive (95% CI; n/N)	Sensitivity: smear-negative (95% CI; n/N)	Sensitivity: HIV-negative (95% CI; n/N)‡	Sensitivity: HIV-positive (95% CI; n/N)‡	Specificity (95% CI; n/N)	Sensitivity (95% CI; n/N)	Specificity (95% CI; n/N)
Xpert	83% (79 to 86; 383/462)	46% (37 to 55; 63/137)§	90% (84 to 94; 143/159)	77% (68 to 84; 88/155)	98% (97 to 99; 960/977)	95% (91 to 98; 167/175)	98% (96 to 99; 369/376)
Xpert Ultra	88% (85 to 91; 408/462)	63% (54 to 71; 86/137)§	91% (86 to 95; 145/159)	90% (83 to 95; 103/115)	96% (94 to 97; 934/977)	95% (91 to 98; 166/175)	98% (97 to 99; 370/376)
Difference (Xpert Ultra minus Xpert)	5.4% (3.3 to 8.0; 25/162)	17% (10 to 24; 23/137)	1.3% (-1.8 to 4.9; 2/159)	13% (6.4 to 21; 15/115)	-2.7% (-3.9 to -1.7; 36/977)	-0.6% (-3.2 to 1.6; 1/175)	0.3% (-0.7 to 1.5; 1/376)

Ultra's overall sensitivity was 5% higher than that of Xpert MTB/RIF

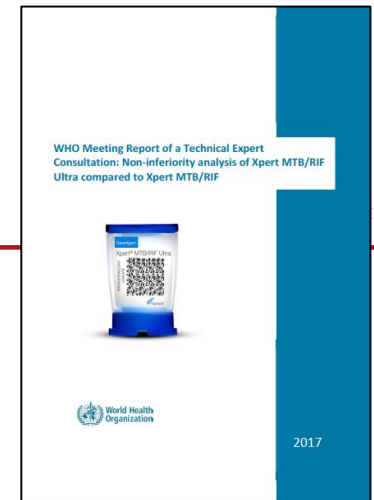
Higher incremental sensitivity among paucibacillary forms of TB:

- 17% higher for smear negative culture positive patients
- 13% higher for HIV positive patients



# WHO recommendations (March 2017)

WHO Technical Expert Group Consultation, January 2017



## Trace calls interpretation:

- Among persons with HIV, children and extrapulmonary specimens\* “trace calls” should be considered to be true positive results;
- Among persons not at risk for HIV, with an initial “trace call” positive result, a fresh specimen from the patient should undergo repeat testing and the result of the second Ultra test be used for clinical decisions and patient follow-up;
- A second “trace call” positive is sufficient to make a diagnosis of pulmonary TB unless there is a recent history of TB;
- Among all persons that test “trace call” positive additional investigations are needed to confirm or exclude resistance to rifampicin.

WHO plans to update policy recommendations supporting the use of Ultra in 2018.  
Cepheid will gradually phase out the current MTB/RIF assay and replace it with Ultra.

## Early detection and treatment of tuberculosis in Europe

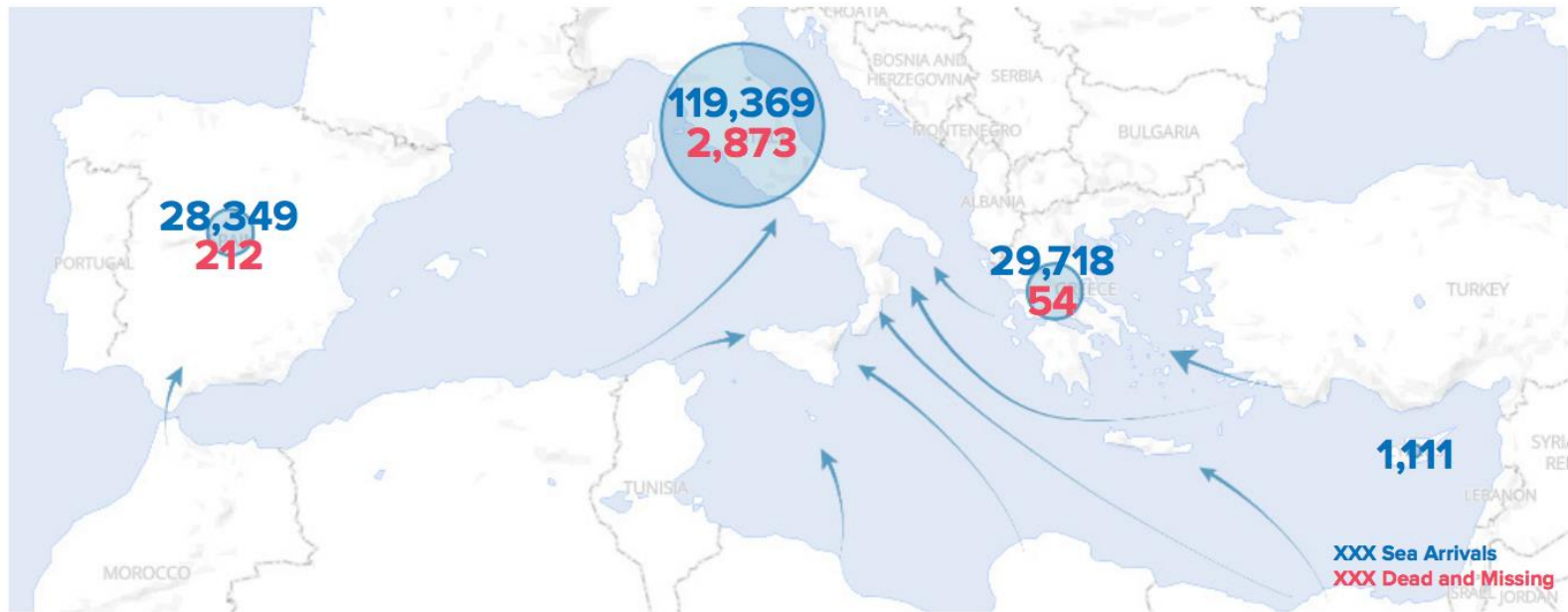
The project aim is to contribute to TB elimination in the EU using **evidenced based interventions** to ensure early diagnosis, improve integrated care and support community and prison outreach activities in low and high-incidence countries.

Prioritized population include migrants, homeless persons, prisoners, problem drug users and those with multi-drug resistant tuberculosis.

# Screening at first arrival in Italy: results from E-DETECT intervention

# Mediterranean Situation

## Arrivals in Europe (2017)



### Arrivals

↓ **178,500<sup>1</sup>** in 2017  
**369,300** in 2016  
**1,015,000** in 2015

### Dead and Missing

↓ **3,139** in 2017  
**5,096** in 2016  
**3,771** in 2015

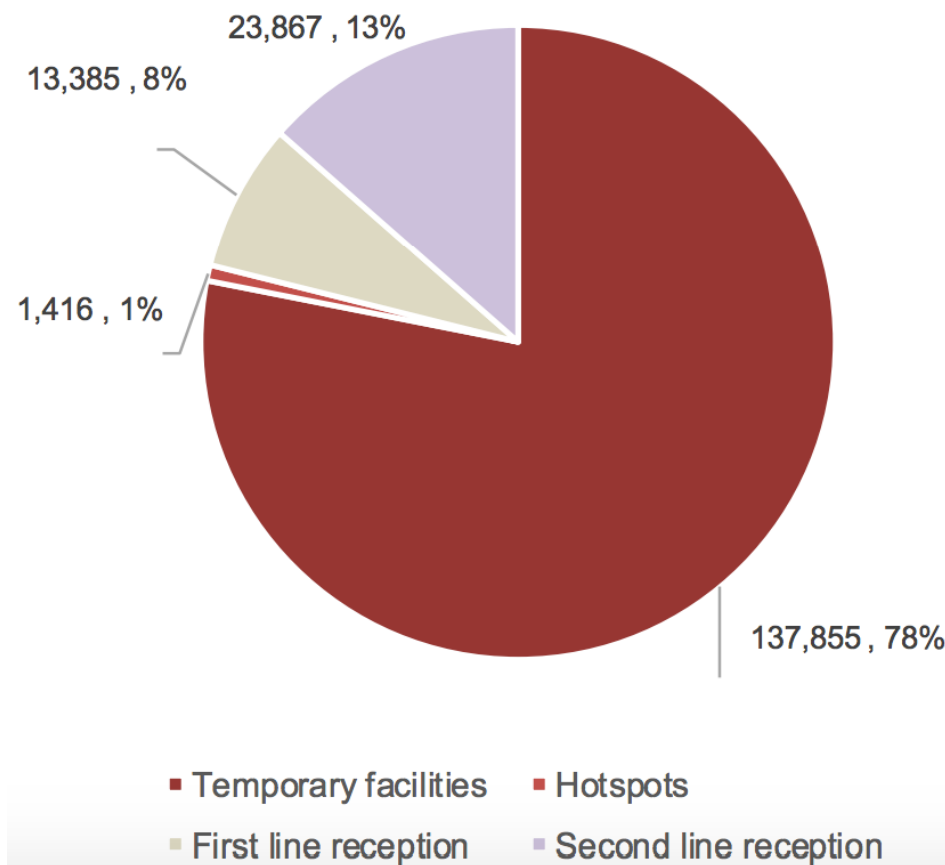
<https://data2.unhcr.org/en/situations/mediterranean>

# Reception and asylum procedures

176,523 persons accommodated in reception centres across Italy

## Italian reception system:

- (1) first assistance facilities (so called CPSA) and hotspots;
- (2) first-line reception facilities (so called CARA);
- (3) second-line reception facilities (SPRAR centres);
- (4) temporary reception centers, also known as extra-ordinary reception centres, or CAS.

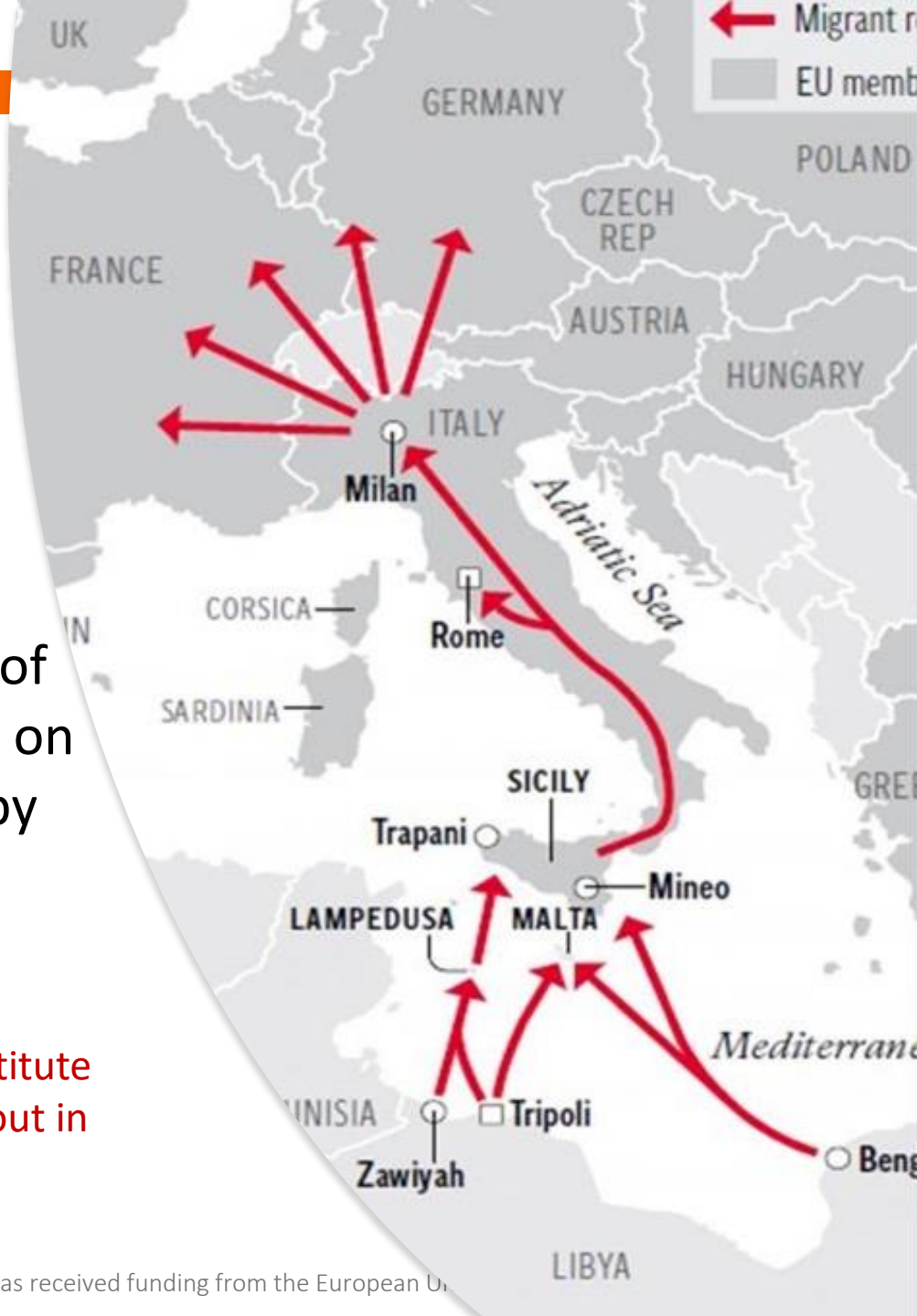


# Temporary settled migrant

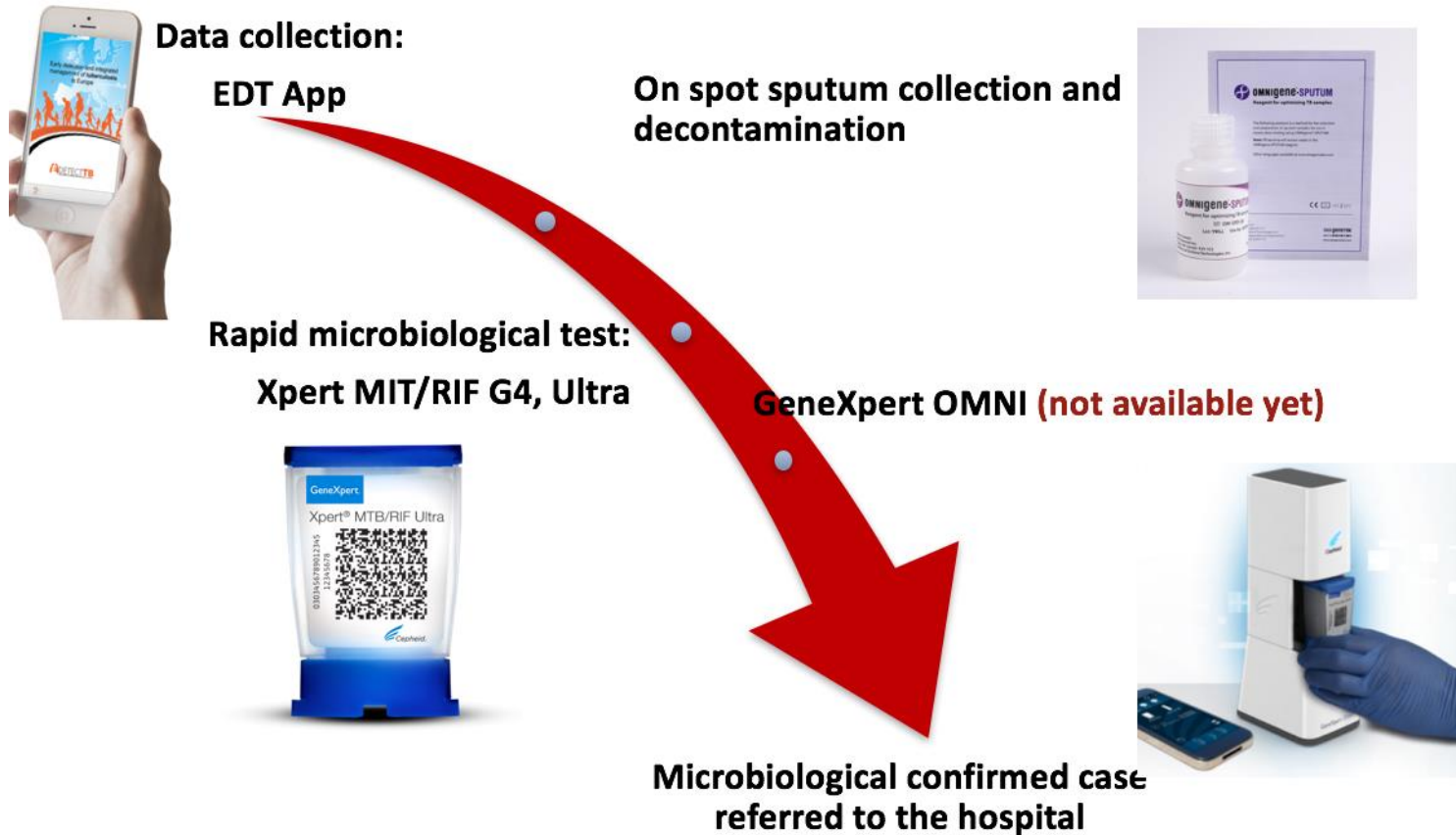
## Aim:

Evaluation of a multi-step strategy for screening migrants of the Mediterranean route based on **symptoms screening** followed by **rapid microbiological diagnosis** for active TB

EDETECT screening activities did not substitute the screening activities routinely carried out in each reception facilities

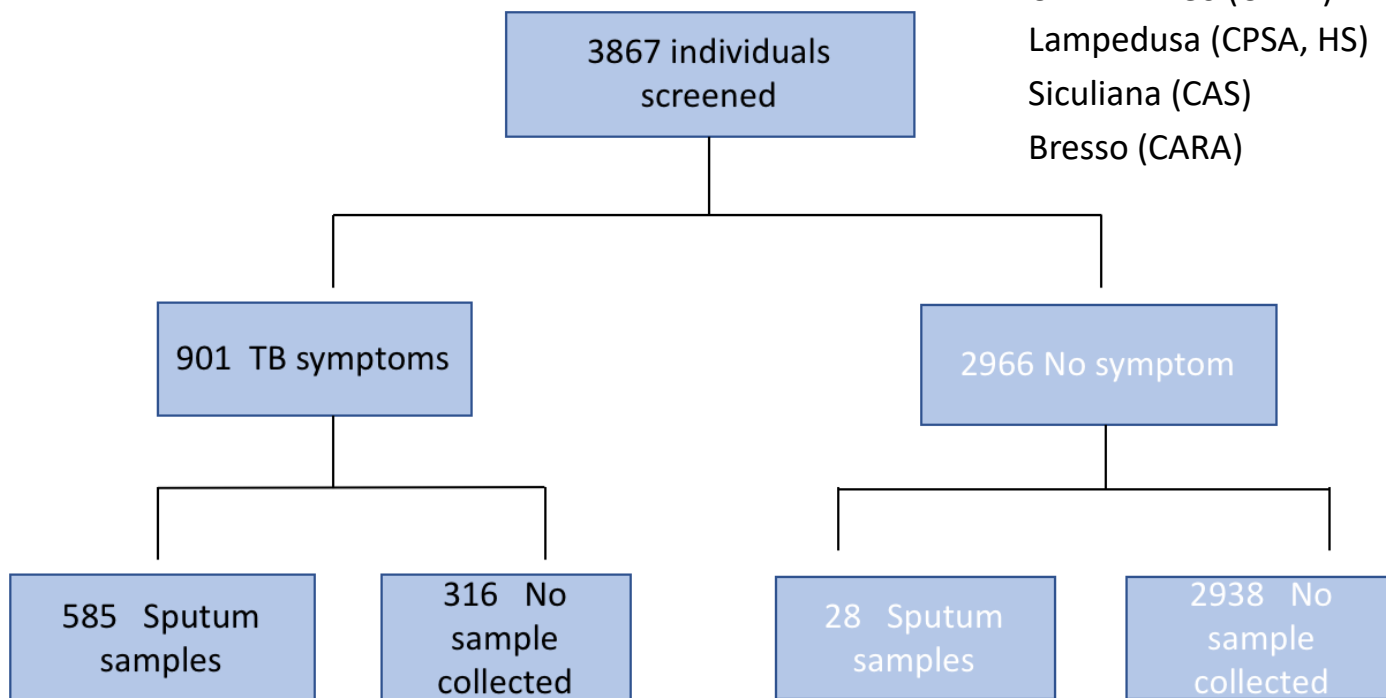


# Active TB screening strategy



# Study flow

Location	N° persons screened	Screening start
CARA Mineo (CARA)	2653 (68,3%)	Nov 2016
Lampedusa (CPSA, HS)	707 (18,3%)	May 2017
Siculiana (CAS)	414 (10,7%)	May 2017
Bresso (CARA)	80 (2,1%)	



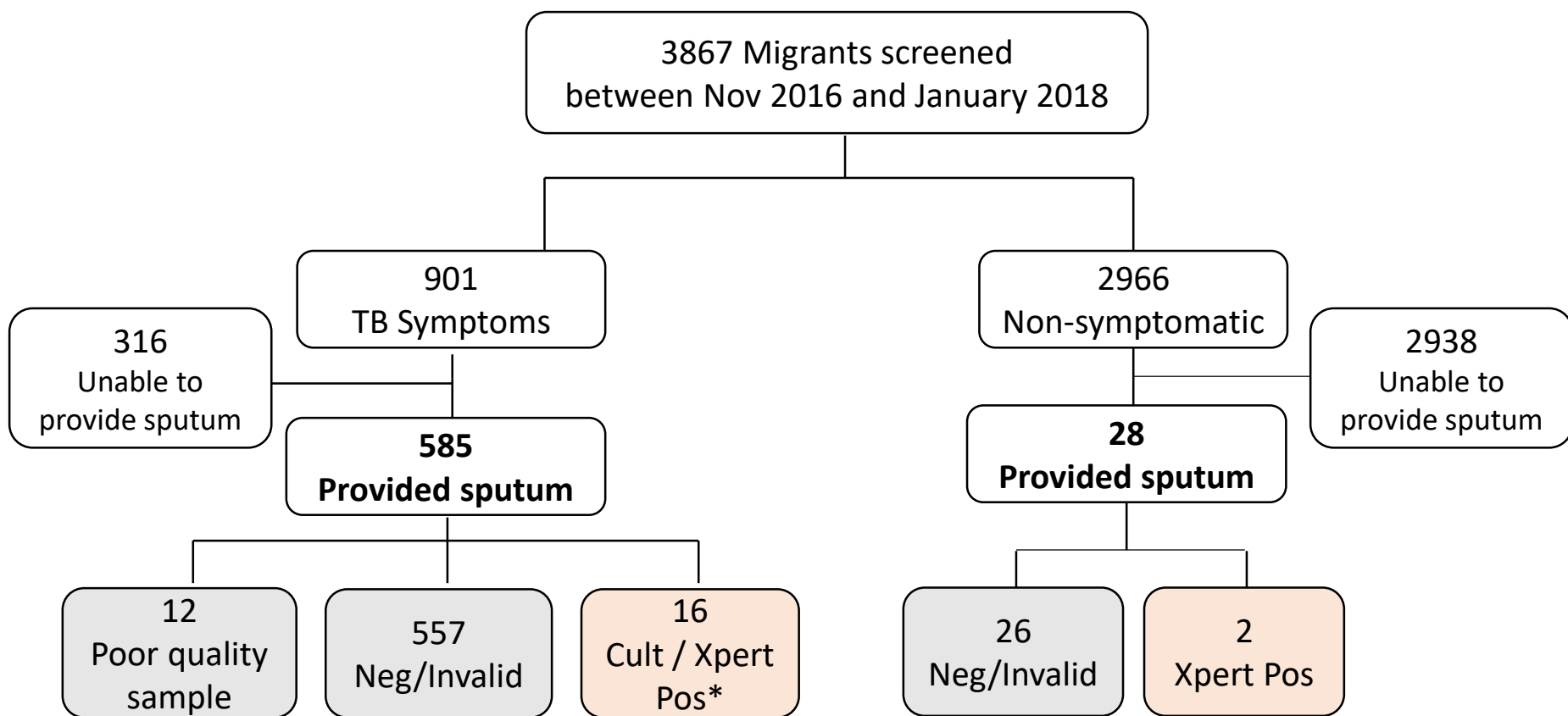


# Study population

Total N 3867	
Age (years) median	22 (19-27)
Male	3343 86.4%
Female	524 13.6%
Lenght of stay in Italy (months)	1 (0-5)
TB incidence in the CoB	
<20	25 0.6%
20-49	294 7.6%
50-149	1220 31.5%
150-249	1438 37.2%
250-349	846 21.9%
350+	34 0.9%
Previous TB	137 3,5%
TB contact	145 3,7%
Cough	496 12.8%
Fever	262 6.8%
Haemoptysis	128 3.3%
Night sweats	220 5.7%
Weight loss	471 12.2%



# TB screening results



\*Culture / XpertMTB/RIF / XpertMTB/RIF Ultra

# TB testing results

Individuals with TB symptoms (16)

**XpertMTB/RIF ULTRA vs Culture**

**XpertMTB/RIF vs Culture**

	<b>Sensitivity (95% CI)</b>	<b>Specificity (95% CI)</b>
<b>XpertMTB/RIF ULTRA</b>	81.8% (52.3-94.9)	99.1% (97.8-99.6)
<b>XpertMTB/RIF</b>	54.6% (28.0-78.7)	99.6% (98.7-99.9)



# Conclusions

- **13 TB confirmed cases** (positive by Culture and/or XpertMTB/RIF): estimated screening yield for active TB among asylum seekers of **336 /100,000**
- XpertMTB/RIF Ultra shows an overall sensitivity higher than Xpert MTB/RIF (82% vs 55%)
- More data are needed on how to interpret Xpert MTB/RIF Ultra “trace calls” (i.e. consider TB treatment history, test repeat results, further clinical assessment, follow up)



# What's next?

## Improving patients access to TB care

### GeneXpert Omni\*



No infrastructure requirements  
Small and Portable.



Proven Cartridge technology



High Connectivity



Integrated Battery

\* Projected availability outside the US end of 2018

# Acknowledgments



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