

# Genomic discrimination between tuberculosis clusters growing because active transmission from those due to reactivations, diagnostic delays or subclinical disease

Cristina Rodríguez-Grande<sup>1,2</sup>, Silvia Vallejo-Godoy<sup>3</sup>, Miguel Martínez-Lirola<sup>4</sup>, Marta Herranz-Martín<sup>1,2</sup>, Sergio Buenestado-Serrano<sup>1,2</sup>, Daniel Peñas-Utrilla<sup>1,2</sup>, Pilar Barroso-García<sup>5</sup>, Senay Rueda Nieto<sup>3</sup>, Francisca Escabias-Machuca<sup>6</sup>, María Teresa Cabezas Fernández<sup>4</sup>, Patricia Muñoz<sup>1,7,8</sup>, Laura Pérez-Lago<sup>1,2</sup>, **Darío García de Viedma**<sup>1,2,7</sup>

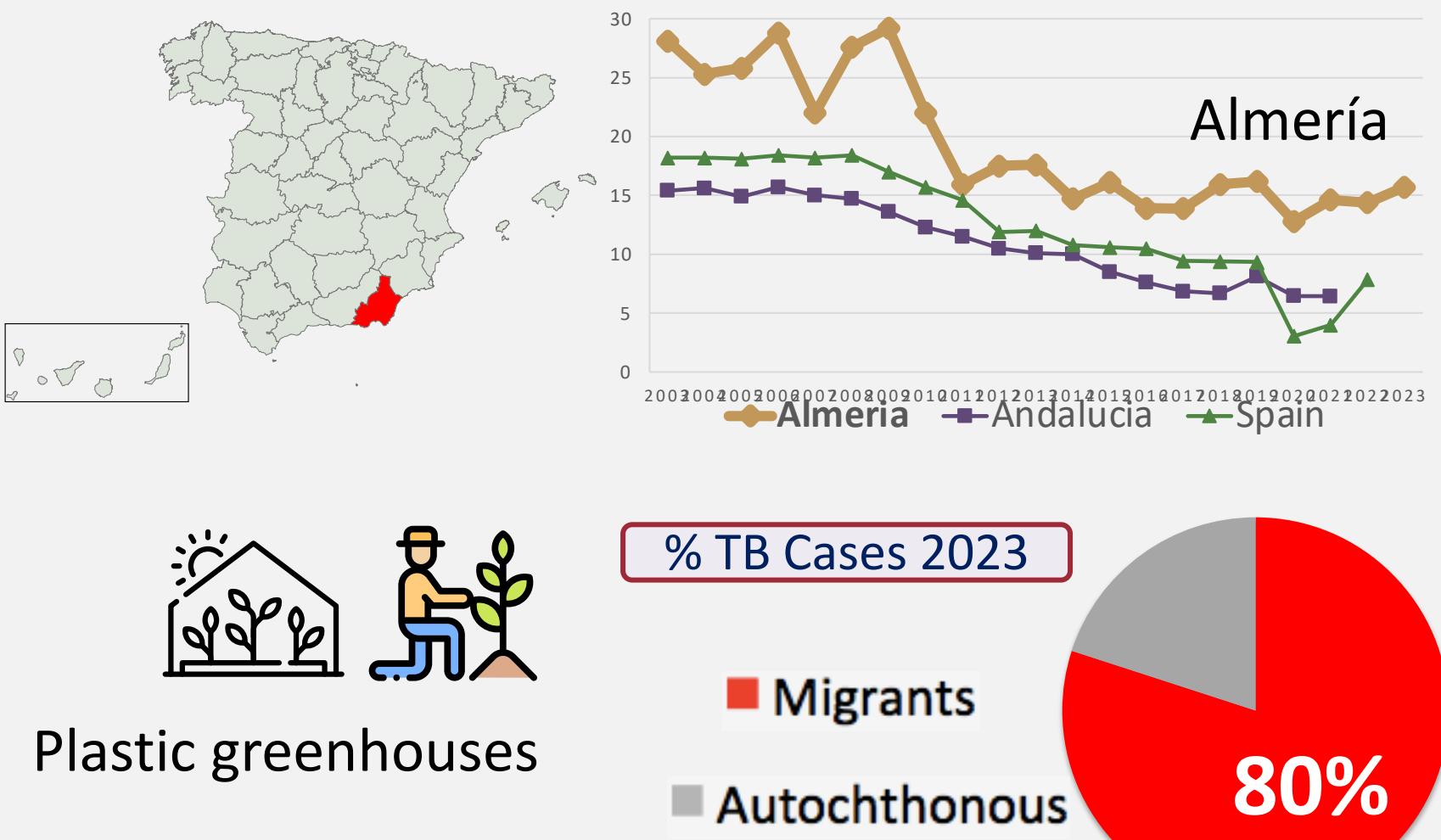


Contact: [dgviedma2@gmail.com](mailto:dgviedma2@gmail.com)

1. Servicio de Microbiología Clínica y Enfermedades Infecciosas, Hos Gen Univ Gregorio Marañón, Madrid, Spain. 2. Instituto de Investigación Sanitaria Gregorio Marañón (IISGM), Madrid, Spain. 3. Serv de Med Preventiva y Salud Pública. H Univ Poniente de Almería, Spain. 4. Complejo Universitario Hospitalario Torrecárdenas, Almería, Spain. 5. Epidemiología. Distrito Sanitario Almería, Spain. 6. Epidemiología.AGS Norte de Almería, Almería, Spain. 7. CIBER Enfermedades Respiratorias (CIBERES). 8. Departamento de Medicina, Universidad Complutense de Madrid, Spain.

## BACKGROUND

### Tuberculosis (TB) incidence in Almería, Andalucía and Spain



## Genomic epidemiology 2003-2023

### Years 2003-2020

#### Quantitative genomic analysis

##### Clusters <12 SNPs

Case	Year	Nationality
Case 1	2018	Mali
Case 2	2019	Mali
Case 3	2021	Mali
Case 4	2022	Mali
Case 5	2022	Senegal

62 CLUSTERS

3-24 cases/cluster

448 clustered cases

### Years 2021-2023

#### New clustered cases

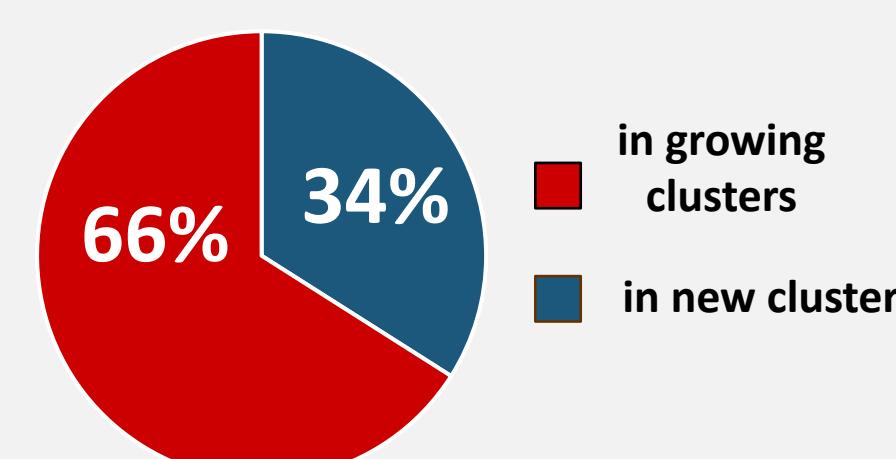
28 GROWING CLUSTERS

1-11 cases entering in preexisting clusters

13 NEW CLUSTERS

2-5 cases/cluster

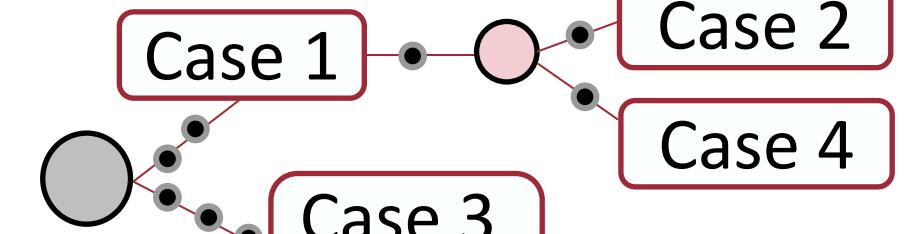
Clustered cases (N: 82)



## Dynamics behind the new clustered TB cases

### Qualitative/Evolutionary genomic analysis

Program Network 5.0



Analysis of the distribution of SNPs between the cases in each cluster

Higher Precision

## New clustered cases due to Recent Active Transmission

Located in the network next to a recently diagnosed case (0-2 SNPs)

### NEW CLUSTERS

Case 1 (2021) Morocco

Case 2 (2021) Spain

84.6%

### GROWING CLUSTERS

48.6%

Mali/Senegal  
Case 1 (2022)  
Case 3 (2022)  
Case 4 (2022)  
Case 5 (2022)  
Case 6 (2022)  
Case 7 (2022)\*  
Case 8 (2022)\*

TRANSMISSION HOT SPOT

Intervention

Identification of new secondary active TB cases \*

## Reasons other than Active recent transmission behind new clustered cases

### New cases due to REACTIVATION

Morocco/Mali/Spain

Case 2 - 2014

Case 3 - 2014

Case 4 - 2015

Case 5 - 2015

Case 6 - 2016

Case 7 - 2016

Case 8 - 2019

Case 9 - 2023

Nigeria

Case 10 - 2017

4 years 0 SNPs

Intervention

LTI profilactic treatment in contacts to limit secondary cases in the future

### Diagnostic delay +/- Subclinical TB

Spain/Nigeria/Senegal

Case 1 - 2006

Case 2 - 2007

Case 3 - 2007

Case 4 - 2008

Case 5 - 2011

12 years 7 SNPs

Evolving viable bacteria?

Slovakia

Case 6 - 2023

Year 2018

Neumologists role: Revision of clinical charts

□ Previous symptoms not attributed to TB

□ X-Ray findings

MonoResistance means a clue for subclinical TB/diagnostic delay

Case 1 (2007) Romania

Case 2 (2008) Romania

Case 1-2 (2014) Romania

9 years 3 SNPs

Mono-FQR

Case 3 (2023) Spain

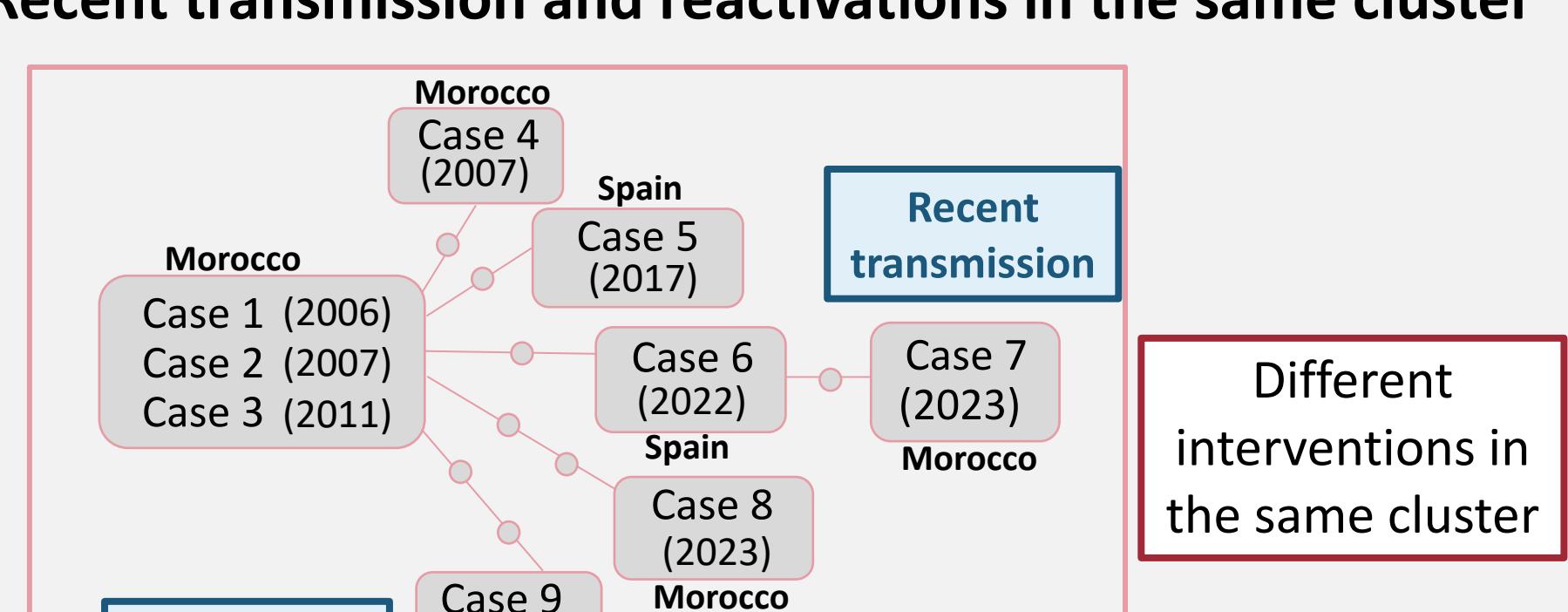
10 cases INH-R

4 cases FQ-R

Currently under study

### Multifactorial

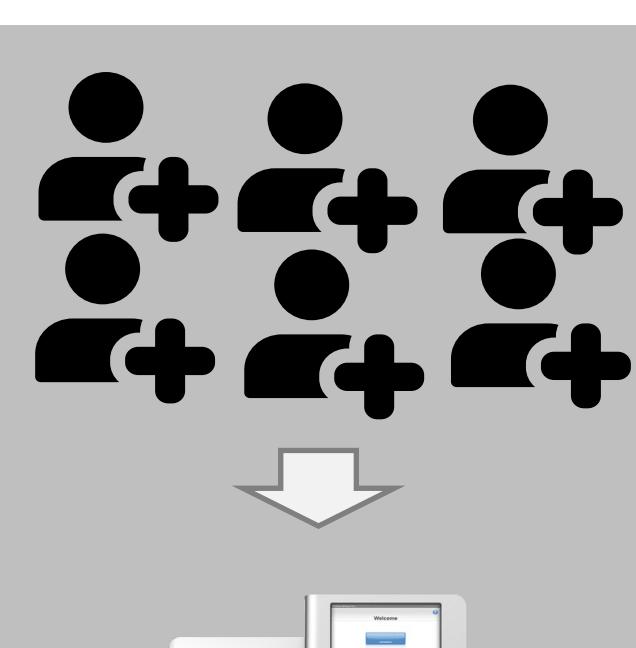
-Recent transmission and reactivations in the same cluster



- Household sequential exposures along diagnostic delay



## YEARS 2003-2020 STANDARD APPROACH

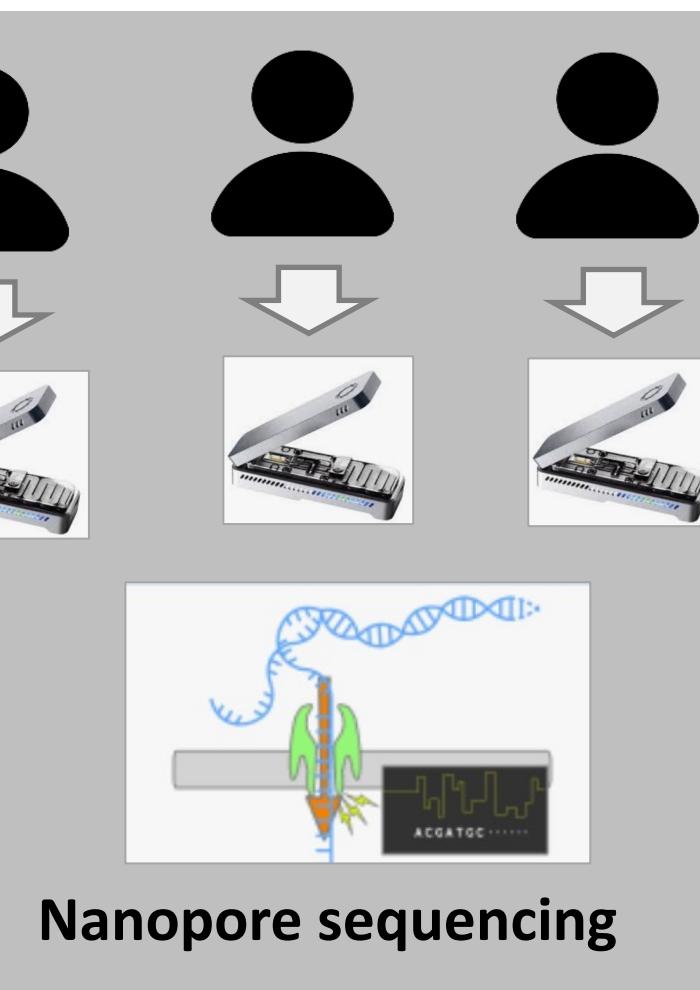


-Pooled in the same run  
-Subcultured isolates

Delayed results

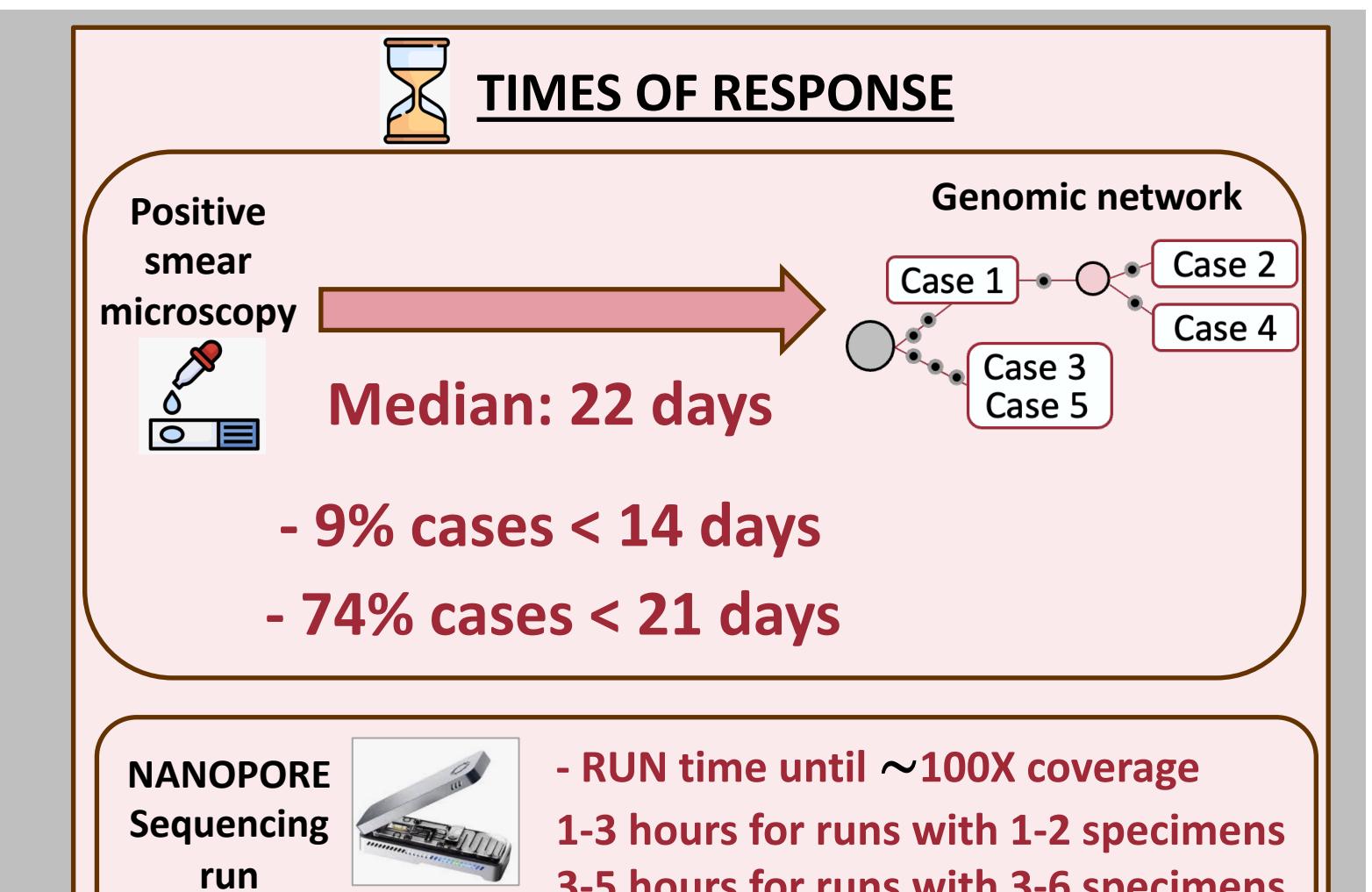
Illumina sequencing  
Short-reads

## YEARS 2021-2023 NEW FASTER STRATEGY



-1 incident case:  
Immediate analysis  
-From primary culture

Faster results



- RUN time until ~100X coverage  
1-3 hours for runs with 1-2 specimens  
3-5 hours for runs with 3-6 specimens