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Original article

Improving tuberculosis management in prisons: impact of a rapid molecular point-of-care test

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Running Title: Tuberculosis point-of-care diagnosis in prison

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1 **Improving tuberculosis management in prisons: impact of a rapid molecular point-**
2 **of-care test**

3

4 **SUMMARY**

5 Objective: To improve tuberculosis (TB) diagnosis in prison, we evaluate the value of the
6 Xpert®MTB/RIF Ultra assay (Xpert) as point-of-care (POC) in a French prison hospital.

7 Methods: We first validated Xpert use on raw sputum at the referent laboratory. Secondly,
8 trained physicians at the prison hospital performed Xpert tests for each patient presenting
9 TB symptoms. The results were compared with Xpert, microscopic examination, culture
10 and drug susceptibility testing on the corresponding decontaminated specimens.

11 Results: 76 inmates were included in 15 months and 21 were diagnosed with TB. The
12 overall sensitivity, specificity, positive and negative predictive values of Xpert were
13 respectively: 92.3%, 100%, 100% and 98.7% on raw sputum. The efficiency of the
14 molecular POC was confirmed by a concordance of 97% between Xpert findings from the
15 prison hospital and culture results. Delay of microbiological diagnosis was reduced by
16 about 18 days for 13 inmates with smear-negative sputum that avoid the mobilization of
17 major means (escort, transport) to perform fibroscopic samples. Repeated Xpert negative
18 results helped to speed the lifting of inmate isolation.

19 Conclusions: The implementation of Xpert in prison could optimize the management of
20 incarcerated patients and thus limit the spread of TB among inmates, carers and other
21 staff.

22

23 **Keywords:** Tuberculosis; prison; Xpert®MTB/RIF Ultra; molecular diagnosis; screening

25 INTRODUCTION

26 Tuberculosis (TB) remains a major global public health problem. In 2018, TB was
27 responsible for about 1.5 million deaths according to the World Health Organization
28 (WHO) with notification of 10 million cases [1]. In Europe, the frequency of TB varies
29 considerably from country to country, mainly in Eastern Europe, with countries reporting
30 rates ranging from 2.6/100,000 in Liechtenstein to 66.2/100,000 in Romania [2]. France
31 reports 5,092 new cases per year and Ile-de-France is the Metropolitan region with the
32 highest incidence rate (16.1 cases per 100,000 inhabitants in 2018) [3]. WHO has
33 developed an action framework in low-incidence countries, such as France, striving to
34 eliminate TB in coming decades and recommends targeting vulnerable groups such as
35 inmates, the homeless, illicit drug users, people with alcohol use disorders, destitute
36 migrants and some indigenous populations and ethnic minorities [4]. In 2018 in France, the
37 reporting rate was nearly 17 times higher among those born abroad than among those
38 born in the country (40.1/100,000 and 2.4/100,000 respectively) with the highest reporting
39 rate among migrants who had arrived in France less than 2 years earlier
40 (312/100,000). The homeless people and prison inmates were also part of a TB-risk
41 population with reporting rates of 249/100,000 and 76/100,000 respectively [3]. Prison
42 inmates have a higher prevalence of communicable diseases such as TB than the general
43 population. Inmates TB prevalence can be up to 50 times higher than national averages. In
44 Europe, the ratio of TB in inmates compared to the general community is estimated, on
45 average, to be 17:1; ranging between 11 times more in western Europe to 81 times more
46 in eastern Europe [6]. In France, the estimated rate of TB notifications was 76 per 100,000
47 inmates in 2018 [3]. A descriptive study was carried out from 2014 to 2018 among inmates

48 at the Fresnes prison centre in Ile-de-France (Paris suburbs). The rate of TB screenings
49 carried out among inmates was high (91%) with an incidence rate of 141.58/100,000 in
50 2018 [7]. The living conditions of imprisonment and the delay in diagnosis and treatment
51 promote the transmission of TB within the prison population as well as within the
52 community through prison staff, visitors and close contacts of released inmates still
53 suffering TB [8–10]. Moreover, the lack of treatment follow up after release or transfer is a
54 risk factor for development of multi-drug resistant TB [11]. In prison, WHO recommends a
55 combination of passive and active screening. Passive case-finding is based on detection
56 of individuals clinically suspected of TB (cough, loss of weight...) while active case-finding
57 involves systematic screening with use of various methods like chest X-rays and rapid
58 molecular tests [12,13]. According to French legislation, TB screening in prison is based
59 on clinical examination followed by a radiological examination if necessary [8]. Inmates
60 with positive TB-screening are sent to a specific prison hospital like the Fresnes National
61 Public Health Establishment (FNPHE), in Ile-de-France, to confirm diagnosis.
62 Microbiological TB diagnosis is based on time-consuming smears and cultures. Nucleic
63 Acid amplification tests (NAATs) allow faster results. In less than 80 minutes, the
64 Xpert[®]MTB/RIF Ultra assay (Xpert) can detect *M. tuberculosis complex* DNA and
65 mutations conferring rifampicin-resistance by targeting the *rpoB* gene [14]. In this
66 perspective, we conducted a study to evaluate the feasibility and the interest of
67 implementing the Xpert assay at prison hospitals to reduce the delay of diagnosis.

68 **MATERIALS AND METHODS**

69 **Study population**

70 Inmates were studied from October 2017 to December 2018. They were recruited from Ile-
71 de-France prisons after a positive TB screening. In the Ile-de-France region, physicians

72 from the penitentiary health units performed systematic chest radiography in addition to
73 clinical screening for all newcomers or inmates suspected of TB. Systematic screening
74 took place within the first eight days of incarceration. A positive TB screening involved
75 chest radiography with abnormalities such as cavitation, parenchymal nodular infiltration,
76 interstitial involvement, calcified parenchymal mass, pleural effusion or thickening. Inmates
77 included were transferred to the prison hospital (FNPHE) for TB diagnosis and
78 management.

79 **Stages of the point-of-care (POC) study**

80 Our study included two steps over 15 months. First, from October 2017 to April 2018, we
81 evaluated Xpert performances on both raw and decontaminated sputa at the core
82 laboratory (Antoine Beclere University Hospital). For each sputum sent by the prison
83 hospital, we first performed Xpert on the raw sample and then used the decontaminated
84 sample for Xpert, microscopic examination and culture. Secondly, we evaluated the use of
85 Xpert at the prison hospital on raw sputa parallel to TB diagnosis at the microbiological
86 core laboratory (from May to December 2018). Three volunteer physicians were trained by
87 the manufacturer to use Xpert assay on a 4-modules GeneXpert equipment. They checked
88 the quality of the sputum and, for each patient with clinical/radiological signs of pulmonary
89 TB, performed an Xpert assay on raw sputum at the prison hospital. The rest of the
90 samples were sent during the working days to the core laboratory for TB diagnosis
91 (including Xpert on decontaminated samples). First results (smear, PCR) were available
92 by the next day. The trained physicians were also in charge of reporting test results to
93 clinical microbiologists by secure messaging and of general maintenance of the instrument
94 (including quality assurance controls). Physicians performed Xpert on all patients' sputa as
95 long as they had doubts about TB infection and until one was positive. This POC practice

96 was carried out in a room 10 meters square dedicated to this specific activity, with a
97 constant ventilation and temperature maintained between 15°C and 30°C, compatible with
98 the conditions for storing reagents and for operating the instrument. The used reagents
99 were discarded in specific potentially infectious waste bin.

100 **Microbiological methods**

101 NAATs: PCR assays were performed using Xpert®MTB/RIF Ultra according to the
102 manufacturer's instructions. The performances were calculated relative to a gold-standard
103 culture.

104 The microbiological determination involved sputum from each inmate taken on reception
105 and processed according to standard methods, including decontamination with N-acetyl-L-
106 cysteine-sodium hydroxide (NAC-PAC®UNITARY™ Alpha-Tech systems), Auramine
107 fluorescence smear microscopy (RAL STAINER®colorator, Fluo Ral ® coloration kit) and
108 culture in Lowenstein–Jensen and liquid MGIT (MGIT960®, BD Diagnostic Systems). A
109 drug sensitivity test (DST) was also performed for positive cultures using phenotypic
110 susceptibility testing SIRE (S: streptomycin, I: isoniazid, R: rifampicin, E: ethambutol) and
111 PZA (pyrazinamide); applying the standard critical concentrations to detect resistances:
112 1.0 and 4.0 µg/ml for S, 0.1 and 0.4 µg/ml for I, 1.0 µg/ml for R, 5.0 and 7.5 µg/ml for E
113 and 100 µg/ml for PZA; BACTEC™ MGIT™ 960 SIRE Kit and BACTEC™ MGIT™ 960
114 PZA Kit (Becton Dickinson) [15]. All these standard procedures were performed following
115 the biosafety measures required for handling *M. tuberculosis* (MTB) in a BSL-3 laboratory,
116 in agreement with the TB laboratory biosafety manual WHO 2012 and the requirements of
117 the COFRAC (the French quality control commission).

118 **RESULTS**

119 **Preliminary study: comparison of Xpert on raw and corresponding decontaminated** 120 **sputa**

121 Over a 7 month-period at the microbiological laboratory, we compared Xpert results on raw
122 and decontaminated sputa from prison hospital inmates with TB symptoms (Table 1).
123 These results were 100% concordant with cultures and 96% with smears (2 Xpert-
124 positive/smear-negative). Only one sample had an initial Xpert “error” result both on the
125 raw and decontaminated sample and a final valid Xpert result after retesting. Three smear-
126 negative sputa were associated with a low PCR detection signal (“very low” or “trace”
127 detection of DNA) and positive cultures for 2 samples. The negative culture was related to
128 a patient with a recent history of TB and discontinued treatment. In total, Xpert results
129 showed a concordance of 94% (45/48) between raw and decontaminated sputa, which
130 allowed us to complete the second part of our study and to implement the Xpert test at the
131 prison hospital.

132 **Implementation of Xpert at the prison hospital**

133 Over an 8-month period, we evaluated the use of the PCR as a POC strategy at the prison
134 hospital parallel to standard TB diagnosis at the microbiological laboratory. We collected
135 152 sputa. Xpert was performed by the 3 physicians of prison hospital (nurses did not wish
136 to participate) on 46 (30%) specimens only due to lack of time and unavailability of staff
137 (Table 2). Forty-two of them had the same Xpert results on raw and decontaminated
138 samples. These results were concordant with cultures at 100% and with smears at 98% (1
139 Xpert-positive/smear-negative). Two sputa with discordant Xpert results were associated
140 with a negative smear, a low PCR detection signal and a positive culture. We had “error”

141 results on 2 raw sputa (4%) and valid results on the decontaminated samples. Excluding
142 the “error” results, whether the test was performed on raw sputa at the prison hospital or
143 on decontaminated sputa in the microbiological laboratory, we found a concordance of
144 97% (43/44) between Xpert and culture results.

145 **Global performances of Xpert**

146 We gathered results of the two previous studies in order to determine the performance of
147 Xpert on raw and decontaminated sputum according to smear results (Table 3). We used
148 the culture as a gold standard. Sensitivity on raw and decontaminated smear-positive
149 sputa was 100%. Negative smear samples were associated with decreased Xpert
150 sensitivity on raw sputum as well as on decontaminated sputum, respectively 85.7% and
151 76.9%. In total, we found Xpert sensitivity of 92.3% and 85.7% respectively on raw and
152 decontaminated sputum and a specificity of 100% on both samples. The positive predictive
153 and negative predictive values calculated from all samples were respectively 100% and
154 98.7% on raw sputum and 100% and 98.3% on decontaminated sputum. Concerning
155 Xpert results on *rpob* gene mutations, we had a concordance of 100% with DST results
156 and no results available on samples with “trace” DNA.

157 **Interest of Xpert implementation in prison hospital**

158 From October 2017 to December 2018, 76 inmates hospitalized at the prison hospital were
159 included. All were newcomers. The male/female ratio was 74/2 and the average age was
160 37-year-old [18-61]. Forty-eight (63%) of them were born outside metropolitan France, 4
161 (5%) had history of TB and 9 (12%) were HIV-infected. Over the studied period, we
162 diagnosed 21 active TB cases (28%) including one case of Multi Drug Resistant (MDR).
163 No miliary TB was observed. Seven patients were clinically asymptomatic (33%) and 14

164 (67%) presented one or more of the common TB symptoms (Table 4). All had abnormal
165 chest X-rays. No correlation was found between the presence of clinical signs and the
166 existence of a cavitation, on chest/X-ray or computed tomography. Regarding smears,
167 only 2 asymptomatic patients had positive smears (29%) compared to 6 patients in the
168 symptomatic group (43%). Smear positive sputa had a mean 10 days delay of culture
169 positivity while the mean delay for smear negative sputa was 18 days (Fig.1). All 21
170 patients had at least one positive Xpert result. Molecular screening of rifampicin
171 susceptibility was available for 83% of TB patients, including the MDR TB.

172 **DISCUSSION**

173 What is expected of a POC test compared to a traditional laboratory test are the three
174 following keys features [16]: The POC test does not need significant laboratory
175 infrastructures or specialized operators. It is easy to use and interpret, and it is able to
176 deliver a rapid and effective diagnosis. Xpert® MTB/RIF Ultra meets these conditions: it is
177 a fast, easy to perform, and sensitive molecular test [14]. Studies carried out in low
178 prevalence settings or countries showed that Xpert would be beneficial and cost-effective
179 for TB diagnosis compared to current strategies [17]. Above all, the same observation was
180 made for Xpert performed on sputum in Russian and Eastern Europe (former Soviet
181 Union) prisons where the prevalence rates of TB is 2.78% and MDR-TB is 0.74% [18]. In
182 TB POC diagnosis raw sputa must be used. in the first part of our study, we demonstrated
183 that the performances of Xpert on raw and decontaminated sputum are similar as already
184 published [19], and that implementation of this NAAT in prison hospitals should be
185 considered. In the second part of our study, three volunteer physicians at the prison
186 hospital were trained. Through an oral interview, they expressed that the test, the
187 instrument and the maintenance were easy to handle. The concordance of 97% of results

188 between Xpert on raw sputum and cultures validates the efficiency of user training and
189 supports our project to implement Xpert for TB diagnosis. As noted, only 30% of collected
190 specimens were tested by a physician due to lack of time or manpower. Over a period of
191 15 months, 76 inmates were screened for TB. We diagnosed 21 cases of infectious TB
192 (28%). All these patients with infectious TB had abnormal chest X-rays but only 67% had
193 suggestive clinical signs. These results showed the pertinence of systematic chest
194 radiography carried out on entry into prison in the Ile-de-France region. In 62% of TB
195 diagnostic cases, smears were negative. Xpert tests were positive in 100% of cases [20].
196 However, some sputa tested on duplicate (raw and decontaminated samples) had only
197 one Xpert positive result. This suggests that it could be advisable to re-test Xpert on
198 sputum after an initial negative result for patients at high risk of TB [21]. Molecular
199 screening of rifampicin susceptibility was available for 83% of TB patients with a
200 concordance of 100% between DST results. This test allowed us to rapidly identify one
201 patient with MDR TB as already described in a recent study [22]. In this study, we also
202 evaluated performances of Xpert MTB/Rif® Ultra on raw and decontaminated sputum
203 according to smear results. Culture results were our gold standard. Sensitivity was 100%
204 on both raw and decontaminated sputum with positive smears and respectively 85.7% and
205 76.9% with negative smears. This decrease of sensitivity on samples with negative smears
206 have already been reported in previous studies [23]. These results highlight the
207 importance of keeping systematic cultures. Regarding all samples included, we showed
208 92.3%, 100%, 100%, 98.7% of sensitivity, specificity, predictive positive and predictive
209 negative values for Xpert tests on raw sputum and respectively 85.7%, 100%, 100% and
210 98.3% on decontaminated sputum. In this study, a systematic inclusion of Xpert test
211 regardless of smear results reduced the delay of diagnosis and treatment by about 18
212 days for inmates tested positive. Such findings highlight the merit or advantages of the

213 POC test compared with traditional tests. Furthermore, repeated negative Xpert results
214 helped to terminate isolation more quickly. In all cases, the valued predictive positive and
215 predictive negative capacities of Xpert precluded mobilization of major means (escort,
216 transport) to perform fibroscopic sampling. Despite the limitations of our results due to the
217 low number of inmates included, these positive feedbacks encourage us to continue the
218 experiment. The next step could be to extend Xpert use at the prison hospital to other
219 types of samples [24]. However, before we can go any further, we need to set up a
220 computer connection between the GeneXpert equipment located in the prison hospital and
221 the core laboratory in order to guarantee rapid and secure result transmission and
222 microbiological validation. According to the WHO action framework in low-incidence
223 countries, Xpert could be extended as the POC test to other vulnerable groups like the
224 homeless and migrants. In London, a mobile health unit has been created to detect TB in
225 these populations, targeting homeless shelters, day centres, street kitchens and drug
226 treatment services using Xpert as the POC test. Patients are first offered a digital chest
227 radiography and sputum is collected for Xpert in the presence of abnormalities consistent
228 with active pulmonary TB [25]. Several studies have shown the value of using ultrasound
229 for pulmonary and extra-pulmonary TB diagnosis [26,27]. Ultrasound could also be an
230 interesting tool as a POC test and a less expensive alternative to digital chest radiography.

231 In conclusion, our study shows that implementation of Xpert as a POC strategy in a French
232 prison hospital improves TB diagnosis in patients with abnormal thoracic X-rays. This fast
233 and easy-to-use molecular biology tool allows an early TB diagnosis from raw sputum,
234 helps initiate appropriate treatment, and prevents the spread of TB and the emergence of
235 MDR-TB. Although cultures remain the gold standard and are essential to DST, Xpert

236 seems to be a promising way to optimize the fight against TB particularly in a prison
237 setting.

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239

240 **Author contributions**

241 DA, DPF, MG and GCC conceived the study. SV managed the technical work in the core
242 laboratory. DA and HL performed the analysis at the POC. GCC, DA, HL and NPL did the
243 preliminary analysis. EM wrote the first draft that was double checked by other authors. All
244 authors approved the final version.

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246 Cepheid industry provides GeneXpert equipment and reagents at FNPHE. The funders
247 had no role in study design, data collection and interpretation, or the decision to submit the
248 work for publication.

249 **Conflict of interest**

250 None of the authors have any conflicts of interest regarding the content of this manuscript.

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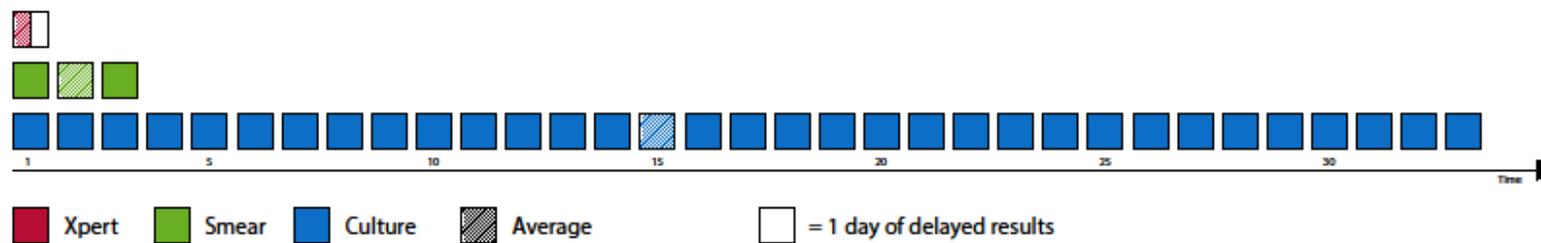


Fig. 1. Delays of positivity of microbiological diagnostic of prison hospital patient's suspected of tuberculosis

Table 1. Comparison of Xpert®MTB/RIF Ultra results on raw and decontaminated sputum (n=48)

Results	Smear		Culture	
	Positive	Negative	Positive	Negative
Raw (laboratory)/ Decontaminated(laboratory) Xpert results				
Positive/positive (n=4)	2	2	4	0
Negative/negative (n=41)	0	41	0	41
Positive/negative (n=2)	0	2	2	0
Negative/positive (n=1)	0	1	0	1
Total	2	46	6	42

Table 2. Comparison of Xpert®MTB/RIF Ultra at the prison hospital (raw sputum) and at the laboratory (decontaminated sputum) (n=46)

Results	Smear		Culture	
	Positive	Negative	Positive	Negative
Raw(prison hospital)/ Decontaminated (laboratory) Xpert results				
Positive/positive (n=5)	4	1	5	-
Negative/negative (n=37)	-	37	-	37
Positive/negative (n=1)	-	1	1	-
Negative/positive (n=1)	-	1	1	-
Error/negative (n=2)	-	2	-	2
Total	4	42	7	39

Table 3. Xpert®MTB/RIF Ultra sensitivity and specificity on the raw and decontaminated sputum

Xpert sensibility and specificity	Smear positive	Smear negative	All samples
Raw sputum (n=94)			
Sensitivity	100%	85.7%	92.3%
	95% CI: 61 - 100%	95% CI: 48.7 - 97.4%	95% CI: 66.7 - 98.6%
Specificity			100%
			95% CI: 95.3 - 100%
Decontaminated sputum (n=200)			
Sensitivity	100%	76.9%	85.7%
	95% CI: 67.6 - 100%	95% CI: 49.7- 91.8%	95% CI: 65.4 - 95%
Specificity			100%
			95% CI: 97.9 - 100%

Table 4. Diagnostic of 21 inmates with TB: clinical, radiological and biological data

X-ray	Asymptomatic patients (n=7)		Symptomatic patients* (n=14)	
	Cavitation	Other abnormalities**	Cavitation	Other abnormalities
Xpert				
positive	6	1	8	6
Auramine				
negative	4	1	3	5
positive	2	0	5	1
Total	6	1	8	6

* Symptoms: fever, night sweats, cough, weight loss

** Other abnormalities: parenchymal nodular infiltration, interstitial involvement, calcified parenchymal mass or pleural effusion or thickening