CASE REPORT: ACQUIRED DISSEMINATED BCG IN THE CONTEXT OF A
DELAYED IMMUNE RECONSTITUTION AFTER HEMATOLOGICAL
MALIGNANCY

SUPPORTING INFORMATION

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MATERIAL & METHODS

Patients and healthy donors

The study was conducted in accordance with the principles of Helsinki declaration. Written informed consents were obtained from the patient as well as from age and gender matched healthy donors (HD).

Phagocytosis assays

The investigation of phagocytosis and of oxidative burst activity were performed at the hospital laboratory (CE/IVD methods PHAGOTEST™, PHAGOBURST™, Celonic) according to the manufacturer’s protocols.

PBMC stimulation and cytokine detection

Heparinized blood samples were collected from HD. Peripheral blood mononuclear cells (PBMC) were separated by density gradient centrifugation. Cells were plated at 10⁶ cells/well in a 24 well-plate containing RPMI supplemented with 10% Fetal Bovine Serum (FBS) and stimulated for 48 hours with phorbol myristate acetate (PMA; 100ng/mL; Invivogen) and ionomycin (1µg/mL; Invivogen), IL12 (100ng/mL; Preprotech), or heat-inactivated patient’s strain of Mycobacterium Bovis bacillus Calmette-Guérin (1 CFU/cell). Culture supernatants were collected from the stimulated PBMCs after 48 hours, and cryopreserved. Later, thawed supernatant was used to measure IFNγ levels by ELISA following the manufacturer’s instructions (Invitrogen).

Intracellular cytokines detection: Protein transport inhibitor cocktail (eBioscience) was added during the last 6 hours of incubation. Surface staining was then performed during 15 minutes at +4°C. Fixation and permeabilization were performed with BD Cytofix/Cytoperm (BD) according to the manufacturer’s recommendations. Samples were incubated with anti-cytokines
antibodies for 30 minutes at +4°C. Cell viability was assessed by initial incubation with Fixable Viability Dye eFluor 780 (eBioscience) following the manufacturer’s protocol.

Cells were acquired on a Gallios flow cytometer (Beckman Coulter) and data analysis was performed using Kaluza software (Beckman Coulter) The following monoclonal anti-human antibodies, purchased from BD Biosciences, were used: CD3 (UCHT1), CD4 (RPA-T4), CD8 (RPA-T8), CD14 (MϕP9), IFNγ (B27), TNFα (MAb11).

**Phospho-STAT1 (pSTAT1) assessment**

Fresh EDTA peripheral blood samples were immediately subjected to density gradient centrifugation to get mononuclear cells suspensions. PBMCs were starved during 16 hours in serum free medium (at 37°C). 0.5*10^6 PBMC were then stimulated for 15 minutes with IFNγ (1000UI/mL (50 ng/mL); Preprotech) or 25% (v/v) HD, patient serum (from different time points). If indicated (i) PBMCs were preincubated 30 minutes at room temperature in the presence of 25% (v/v) HD or patient serum (from different time points) and washed before IFNγ stimulation, or (ii) PBMC were stimulated with a solution containing IFNγ preincubated 30 minutes at room temperature with 25% (v/v) HD or patient serum (from time points). Cells were then labeled for pSTAT-1(Y720) and surface markers using BD Phosflow™ Fix Buffer I and BD Phosflow™ Perm Buffer III (BD Biosciences) following the manufacturer’s recommendations. The cells were acquired on a Gallios flow cytometer (Beckman Coulter) and data analysis was performed using Kaluza software (Beckman Coulter) The following monoclonal anti-human antibodies, purchased from BD Biosciences, were used: CD3 (UCHT1), CD4 (RPA-T4), CD14 (MϕP9), STAT1-pY701 (4a).

**Whole Genome Sequencing (WGS) of M. bovis BCG strain and phylogenomic analysis**
The *M. bovis* BCG strain was sent to the French National Center for Mycobacteria (NRC-MyRMA) for expertise. Total genomic DNA was extracted using the geneLEAD VIII (Diagenode Diagnostics®) automated DNA extractor from isolate grown on Löwenstein-Jensen medium. Preparation of paired-end libraries using an Illumina Nextera XT kit (Illumina, San Diego, CA, USA) and Illumina NextSeq 550 WGS sequencing were done by the sequencing platform P2M-PIBnet (Institut Pasteur, Paris, France) following manufacturer’s recommendations. The raw data of Illumina sequencing reads have been deposited in the National Center for Biotechnology Information (NCBI) Sequence Read Archive (SRA) database (SRA accession number SRR13767788, BioProject ID PRJNA704236).

The WGS raw data were analyzed with BioNumerics 7.6® (Applied Maths) and on the Galaxy server. The quality of paired end reads was checked with FastQC (version 0.11.7).

The genomes of the vaccinal *M. bovis* BCG strains, *M. bovis* reference genome AF2122/97 were downloaded from PATRIC (https://www.patricbrc.org/) for genomic comparison and phylogenetic analysis. Alignment of protein sequences was performed with MUSCLE and CDS nucleotide sequences (1000 genes) with BioPython (Codon_align function). The Bootstrapping analysis was realized with RAxML (x100). The phylogenetic tree was generated according to the Maximum Likelihood method and visualized and annotated on iTOL (Interactive Tree of life) (https://itol.embl.de).

**Whole Exome Sequencing**

As previously described (1), genomic DNA was isolated from patient’s and parents’ whole peripheral blood using standard protocols. Exome sequencing libraries were prepared with the Twist Library preparation kit and captured with Human Core Exome probes extended by Twist Human RefSeq Panel (Twist Bioscience, San Francisco, CA) following the manufacturer’s recommendations. Paired-end (2 × 75 bp) sequencing was performed on a NextSeq500
sequencer (Illumina, San Diego, CA). Before any processing, quality control was performed
using FastQC. The raw reads data were next mapped using the Burrows-Wheeler Alignment
(BWA) tool. Average target read coverage was at least 60-fold. After read mapping, further
quality indicators were calculated from the resulting BAM file using SAMtools, Qualimap.
Variant calling was done using the GATK HalotypeCaller of the GATK software suite. The
annotation was performed by VEP, the Ensembl Variant Effect Predictor. We focused only on
protein-altering variants (missense, nonsense, splice site variants and coding indels) with
alternative allele frequencies < 0.005 in the 1000 Genomes Project, the Genome Aggregation
Database (gnomAD) and an internal exome database including ~1000 exomes.
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FIGURE S1. Clinical history of the patient. Post-colectomy 18F-FDG-TEP-CT-scan revealing a hematological malignancy (OMS 2008 grade 1-2 follicular lymphoma), diagnosed 3 years before being referred to our department, and involving the lachrymal gland and the bowel.
### TABLE S1. Clinical and biological parameters

BCGosis: disseminated BCG disease; CRF: C reactive protein; GFR (MDRD): glomerular filtration rate using the modification of diet in renal disease equation; G-CSF: granulocyte-colony stimulating factor; IgIV: Intravenous immunoglobulin

|                | 2017                          | 2018       | 2019       | 2020       | 2021       |
|----------------|-------------------------------|------------|------------|------------|------------|
|                | 06-13 | 12-01 | 02-01 | 07-23 | 08-02 | 09-12 | 09-27 | 10-10 | 10-26 | 11-02 | 11-07 | 12-15 | 01-11 | 02-22 | 03-29 | 06-07 | 08-08 | 11-22 | 03-10 | 03-10 | 25-01 |
| Leucocytes     | 4000-10500 | 5100 | 3950 | 4010 | 3980 | 3160 | 1980 | 2210 | 3250 | 2070 | 2350 | 5760 | 6490 | 5620 | 3500 | 3170 | 3190 | 2990 | 3680 | 4540 |
| Neutrophils    | 1800-7700 | 3060 | 1580 | 1640 | 2480 | 1570 | 1970 | 4900 | 5170 | 4740 | 2430 | 2310 | 2410 | 2150 | 2510 | 3370 |
| Monocytes      | 100-1000 | 160  | 170 | 360 | 260 | 210 | 430 | 750 | 410 | 450 | 470 | 430 | 390 | 500 | 360 |
| Lymphocytes    | 1600-2400 | 530  | 320 | 240 | 190 | 230 | 190 | 200 | 510 | 510 | 420 | 550 | 360 | 360 | 466 | 671 | 618 |
| CD3+           | 1100-1700 | 197  | 148 | 228 | 174 | 269 | 456 | 366 | 489 | 317 | 316 | 384 | 513 | 419 |
| CD4+           | 700-1100 | 119  | 83 | 127 | 102 | 162 | 283 | 222 | 293 | 186 | 195 | 231 | 296 | 206 |
| CD8+           | 500-900 | 49  | 30 | 42 | 38 | 60 | 81 | 72 | 77 | 55 | 55 | 72 | 99 | 76 |
| CD19+          | 200-400 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 31 | 71 | 127 |
| NK cells       | 200-400 | 5 | 6 | 6 | 16 | 42 | 45 | 57 | 37 | 26 | 25 | 49 | 76 |
| IgG            | 7.20-14.70 | 8.52 | 7.67 | 5.5 | 7.21 | 8.27 | 7.93 | 8.93 | 8.74 | 8.96 | 8.24 | 8.53 |
| IgA            | 1.10-3.60 | 1.06 | 0.91 | 1.04 | 1.07 | 1.01 | 1.01 | 0.81 | 0.82 | 0.96 | 0.86 | 0.86 |
| IgM            | 0.48-3.10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.19 |
| C reactive protein | <4 | mg/L | 38 | 35 | 26 | 31 | 24 | 25 | 58 | 40 | 24 | 11 | 4.1 | 0 | 6 | 10 | 7 | 6.9 | 19.6 | 8.9 |
| GFR (MDRD)*    | >90 | ml/min | 86 | 67 | 53 | 32 | 32 | 26 | 20 | 39 | 46 | 49 | 48 | 53 | 48 | 49 | 51 | 49 | 53 | 53 | 64 | 60 |
| Creatininemia  | 64-104 | µmol/L | 208 | 206 | 242 | 227 | 172 | 152 | 144 | 146 | 153 | 145 | 143 | 139 | 144 | 133 | 133 | 133 | 133 | 115 | 120.7 |
| Proteinuria    | 0.86 | 0.90 | 0.82 | 0.49 |
| BCGosis        | YES | YES | YES | YES | YES | YES | YES | YES | YES | YES | NO |
| Pneumocystosis (PCR+) | YES | YES | YES | YES | YES | YES | YES | YES | YES | YES | NO |
| Imukin (recombinant interferon-γ1b) | YES | YES | YES | YES | YES | YES | YES | YES | YES | YES | NO |
| G-CSF therapy  | YES | YES | YES | YES | YES | YES | NO | YES | NO |
| IVIg           | YES | YES | YES | YES | YES | YES | YES | YES | YES | YES | NO |
| Antibiotherapy of tuberculosis | YES | YES | YES | YES | YES | YES | YES | YES | NO | NO | NO |
# TABLE S2. Inborn errors of immunity genes prioritized in WES analysis

| Gene  |...|...|...|...|...|...|...|...|
|-------|---|---|---|---|---|---|---|---|
| ACP5  | CD20 (MS4A1) | DNAJC21 | IKZF1 | MASP2 | PRF1 | SLC35C1 | TNFSF6 (FASL) |
| ACTB  | CD21 (CR2)   | DOCK2   | IKZF2 | MCM4  | PRKCD | SLC37A4  | TPP1         |
| ADA   | CD247        | DOCK8   | IKZF3 | MEFV  | PRKDC | SMAD9    | TPP2         |
| ADAM17| CD27         | EFL1    | IKZF4 | MKL1   | PSEN  | SMAD9L   | TRAC (TCRa)  |
| ADAR1 | CD3D         | EIF2AK3 | IKZF5 | MOGS  | PSENEN | SMARCA1  | TRAF3       |
| AICDA | CD3E         | ELANE   | IL10  | MSH6  | PSMA3 | SMARCD2  | TRAF3IP2 (ACT1) |
| AIRE  | CD3G         | EPG5    | IL10RA| MSN (Moesin) | PSMB4 | SP110    | TREX1         |
| AK2   | CD40         | ERCC6L2 | IL10RB| MST1 (STK4) | PSMB8 | SPINK5   | TRNT1         |
| API53 | CD40L        | EXTL3   | IL12B | MTHFD1| PSMB9 | SRP54    | TTC37        |
| AP3B1 | CD45         | FAAP24  | IL12RB1| MVK | PSMG2 | SRY      | TTC7A        |
| AP3D1 | CD46         | FADD    | IL17F | MYD88 | PSTPIP1 (C2BP1) | STAT1 | TYK2 |
| ARHGAP10 | CD55 | FAM105B (OTULIN) | IL17RA | MYSM1 | PSTPIP1 | STAT2 | UNC13D |
| ARHGAF1 | CD59 | FASLG | IL17RB | NBEAL2 | PTEN | STAT3 | UNC93B1 |
| ARHGAF28 | CD70 (TNFSF7) | FAT4 | IL17RG | NBS1 | PYCARD | STAT5B | UNG |
| ARHGAF4 | CD79a | FCGR3A (CD16) | IL1RN | NCF1 | RAB27A | STIM1 | USB1 |
| ARPC1B | CD79b | FCN3 | IL21 | NCF2 | RAC2 | STN1 | USP18 |
| ATM   | CD81         | FERMT3  | IL21R | NCF4 | RAG1 | STX11 | VPS13B |
| ATP6AP1 | CD8A | FEZF2 | IL2RA (CD25) | NCKAP1L | RAG2 | STXB2P2 | VPS45 |
| BACH2 | CEBPE        | FHL1 (COL1A2) | IL2RG | NCSTN | RASGRP1 | TAP1 | WAS |
| BCL10 | CECR1 (ADA2) | FOXN1 | IL36 | NEMO (IKBKG) | RBCK1 | TAP2 | WDR1 |
| BCL11B | CFB | FOXP3 | IL36RN | NFAT5 | RELA | TAPBP | WIPF1 |
| BLM (RECQL3) | CFD | FPR1 | IL7R | NFKB1 | RELB | TAZ | XIAP |
| BLNK  | CFH | G6PC3 (SNC4) | INO80 | NFKB2 | RFX5 | TBK1 | ZAP70 |
| BTK   | CFHR1-5      | G6PD   | IRAK1 | NHEJ1 | RFXANK | TBX1 | ZNF341 |
| C1QA  | CFI | G6PT1 | IRAK4 | NHP2 | RFXAP | TCF3 |
| C1QB  | CFP | GATA1 | IRF2BP2 | NIK (MAP3K14) | RHOD | TCI1G1 |
| C1QC  | CHD7         | GATA2 | IRF3 | NLR4C | RIPK1 | TCN2 |
| C1R   | CIITA        | GFI1   | IRF7 | NLRP1 | RLTPR (CARMIL2) | TERC |
| C1S   | CLEC7A (Dectin-1) | GINS1 | IRF8 | NLRP12 | RMRP | TERT |
| C2    | CLPB         | GINS1 | ISG15 | NLRP3 | RNASEH2A | TFRC |
| C3   | COPA   | HAX1 | ITCH  | NOD2  | RNASEH2B | THBD  |
|------|--------|------|-------|-------|----------|-------|
| C4A  | CORO1A | HMOX | ITGB2 | NOP10 | RNASEH2C | THPO  |
| C4B  | CSF2RA | HOIL1| ITK   | NSMCE3| RNF168   | TICAM1|
| C5   | CSF2RB | HOIP | JAGN1 | ORAI-1| RNU4ARAC | TINF2 |
| C6   | CSF3R  | HYOU1| JAK1  | OTULIN| RORc     | TIRAP |
| C7   | CTC1   | ICF1 | JAK2  | OX40  | RPSA     | TLR3  |
| C8A  | CTLA4  | ICF2 | JAK3  | PARN  | RTE1     | TLR7  |
| C8B  | CTPS1  | ICF3 | KDM6A | PEPD  | RUNX1    | TLR9  |
| C8G  | CTSC   | ICF4 | KMT2D | PGM3  | SAMHD1   | TMC6  |
|      |        |      |       |       |          | (EVER1)|
| C9   | CXCR2  | ICOS | LAMTOR| PIK3CD| SBDS     | TMC8  |
|      |        |      |       |       |          | (EVER2)|
| CARD11 | CXCR4 | IFIH1| LAT   | PIK3R1| SCL46A1  | TMEM173|
|      |        |      |       |       |          | (Sting)|
| CARD14 | CXCR5 | IFNAR2| LCK   | PLCG2 | SLC39A7  | TNFAIP3|
|      |        |      |       |       |          | (A20)  |
| CARD9 | CYBA   | IFNGR2| LIG1  | PMS2  | SEC61A1  | TNFRSF13B|
|      |        |      |       |       |          | (TAC1) |
| CASP10 | CYBB  | IFNGR2| LIG4  | PNP   | SEMA3E   | TNFRSF13C|
|      |        |      |       |       |          | (BAFFR) |
| CASP8 | DCLRE1B| IGFR2| LYST  | PNP   | SERPING1 | TNFRSF1A|
| CBL  | DCLRE1C| IGKC | LRBA  | POLE  | SH2D1A   | TNFRSF6|
|      |        |      |       |       |          | (FAS)  |
| CCBE1 | DDX58 | IGLL1| LYST  | POLE2 | SH3BP2   | TNFSF12|
|      |        |      |       |       |          | (TWEAK) |
| CD19 | DKC1   | IKBA | MAGT1 | POMP  | SLC29A3  |       |
| Reference | Age/Gender | Clinical features | Chemotherapy regiment or immunosuppressive agent | Microbiological identification and histological features | Type of BCG contamination |
|-----------|------------|-------------------|-----------------------------------------------|-----------------------------------------------------|---------------------------|
| Meije et al. Clinical infectious diseases 2017 (2) | 77y, male | - Colon cancer  
- Delay between chemotherapy and infection: 8 years  
- Lung infection (nodules) | ND | Positive PCR and culture in bronchio-alveolar lavage and catheter | Cather-related BCG infection (Onco-Tice strain) |
| Meije et al. Clinical infectious diseases 2017 (2) | 47y, male | - Testicular cancer  
- Delay between chemotherapy and infection: 9 months  
- Lung infection (nodules) | ND | Positive PCR and culture in bronchio-alveolar lavage and catheter  
Non necrotizing granulomas on liver biopsy | Cather-related BCG infection (Onco-Tice strain) |
| Meije et al. Clinical infectious diseases 2017 (2) | 71y, female | - Ovarian cancer  
- Delay between chemotherapy and infection: 8 years  
- Lung infection (nodules) | ND | Positive PCR and culture in bronchio-alveolar lavage  
Non-necrotizing granulomas open air lung biopsy | Cather-related BCG infection (Onco-Tice strain) |
| Meije et al. Clinical infectious diseases 2017 (2) | 69y, female | - Breast cancer  
- Delay between chemotherapy and infection: 8 years  
- Lung infection (nodules and infiltrates) and liver nodules | ND | Positive bacilloscopy on transbronchial biopsy and on catheter exudate  
Positive PCR and culture in bronchio-alveolar lavage and catheter  
Non-necrotizing granulomatous interstitial pneumonitis on transbronchial biopsy | Cather-related BCG infection (Onco-Tice strain) |
| Meije et al. Clinical infectious diseases 2017 (2) | 80y, male | - Colon cancer  
- Delay between chemotherapy and infection: 2 years  
- Lung infection (condensation) | ND | Positive culture in sputum and bronchio-alveolar lavage  
Non-necrotizing granulomatous interstitial pneumonitis on transbronchial biopsy | Cather-related BCG infection (Onco-Tice strain) |
| Meije et al. Clinical infectious diseases 2017 (2) | 73y, female | - Breast cancer  
- Delay between chemotherapy and infection: 6 years  
- Lung infiltrates | ND | Positive culture in bronchial aspirates and lavage | Cather-related BCG infection (Onco-Tice strain) |
| Reference | Age, Gender | Diagnosis | Delay between chemotherapy and infection | Findings | Comments |
|-----------|-------------|-----------|------------------------------------------|----------|----------|
| Meije et al. Clinical infectious diseases 2017 (2) | 68 y, female | Breast cancer | 4 years | Positive PCR and culture in bronchoalveolar aspirate and positive culture in culture Necrotizing granulomatous pneumonitis on transbronchial biopsy | Cather-related BCG infection (Onco-Tice strain) |
| Meije et al. Clinical infectious diseases 2017 (2) | 56 y, male | Colon cancer | 10 months | Positive culture in bronchoalveolar aspirate Necrotizing granulomatous pneumonitis on transbronchial biopsy | Cather-related BCG infection (Onco-Tice strain) |
| Meije et al. Clinical infectious diseases 2017 (2) | 62 y, female | Breast cancer | 1 year | Positive culture in bronchoalveolar aspirate and transbronchial biopsy Necrotizing granulomas on transbronchial biopsy | Cather-related BCG infection (ImmunoCyst® strain) |
| Copes MJ et al. Clin Infect Dis 1992 (3) | 6 y, female | Acute lymphoblastic leukemia | 1 year | Chemotherapy (Berlin-Frankfurt-Munster 1981 protocol) Positive identification of acid-tast bacilli on brain biopsy Positivity of PCR in brain biopsy specimen | Not found |
| Stone MM et al. New England Journal of Medicine 1995 (4) | 3 y, female | Acute lymphoblastic leukemia | 10 months | Chemotherapy (vincristine, prednisone, mercaptopurine, methotrexate as maintenance therapy at the time of BCGosis diagnosis) Positive culture of cutaneous abscess Positive culture of the cerebrospinal fluid | Not found |
| Stone MM et al. New England Journal of Medicine 1995 (4) | 5 y, male | Acute lymphoblastic leukemia | - BCG meningitisid | Chemotherapy (vincristine, prednisone, mercaptopurine, methotrexate as maintenance therapy at the time of BCGosis diagnosis) Positive culture of cerebrospinal fluid | Not found |
| Waecker NJ et al. Clin Infect Dis 2000 (5) | 2.5 y, male | Down syndrome and acute megakaryocytic leukemia in remission | | Chemotherapy | Positive culture of lung biopsy | Not found |
| Waecker NJ et al. Clin Infect Dis 2000 (5) | 13 y, female | Acute lymphocytic leukemia | Remission for 32 weeks since the BCGosis | Chemotherapy | Skin abscess positive to BCG in culture and positivity of direct exam of the | Not found |
| Study Authors | Age | Sex | Diagnosis | Treatment | Bacterial Source | Infection | Comment |
|---------------|-----|-----|-----------|-----------|-----------------|-----------|---------|
| Waeccker NJ et al. Clin Infect Dis 2000 (5) | 6y, male | - Acute lymphoblastic leukemia under maintenance therapy (mercaptopurine and methotrexate) | Chemotherapy | Epidural abscess with positive direct examination and positivity of culture to M. bovis | Not found |
| Vos MC et al. J Infect Dis 2003 (6) | 11y, female | - Acute lymphoblastic leukemia under chemotherapy and intrathecal instillation - Meningitidis due to BCGosis | Chemotherapy | Positive culture of the cerebrospinal fluid with BCG | Nosocomial (cross contamination with onco-tice during the preparation of the cytotoxic agents used as chemotherapy) |
| Vos MC et al. J Infect Dis 2003 (6) | 13y, female | - Hodgkin disease - Disseminated BCGosis | Chemotherapy | Granuloma in lung biopsy and positive culture of BCG strain in lung biopsy | Nosocomial (cross contamination with onco-tice during the preparation of the cytotoxic agents used as chemotherapy) |
| Vos MC et al. J Infect Dis 2003 (6) | 39y, female | - Disseminated BCGosis | Chemotherapy | ND | Nosocomial (cross contamination with onco-tice during the preparation of the cytotoxic agents used as chemotherapy) |
| Vos MC et al. J Infect Dis 2003 (6) | 30y, male | - AIDS, Burkitt lymphoma - Meningitidis due to BCGosis and disseminated BCGosis | Chemotherapy | Positive culture in the cerebrospinal fluid | Nosocomial (cross contamination with onco-tice during the preparation of the cytotoxic agents used as chemotherapy) |
| Vos MC et al. J Infect Dis 2003 (6) | 4y, female | - Pre-B cell acute lymphatic leukemia | Chemotherapy | Positive culture in bronchoalveolar lavage, granuloma in the bone marrow and positive direct analysis of the bone (osteomyelitis) | Nosocomial (cross contamination with onco-tice during the preparation of the cytotoxic agents used as chemotherapy) |

BCG: Bacillus Calmette and Guerin; BCGosis: disseminated BCG disease; ND: no data; AIDS: acquired immunodeficiency syndrome