Risk-assessment may improve selection of patients with suspected sepsis for rapid diagnostics

Logan Ward[1,2], Michela Fantini[3], Vittorio Sambri[3], Steen Andreassen[1,2]

1. Treat Systems ApS, Aalborg, Denmark; 2. Aalborg University, Aalborg, Denmark; 3. Greater Romagna Area Hub Laboratory, Cesena, Italy

24 April 2017

27th ECCMID Vienna, Austria 22 – 25 April 2017

Background

- Rapid diagnostic techniques have the potential to improve patient care, but cost is an issue

- Choosing the right patients for testing – “enrichment” of the testing population to obtain a higher fraction of positive blood cultures (BC+) or positive PCR (PCR+)
  - True positive test results create an opportunity for earlier covering treatment
  - Severely ill/high-risk patients will benefit most from this opportunity

- Setting = Emergency Department
- Rapid diagnostics = pathogen ID and resistance markers direct from primary blood samples e.g. multiplex PCR

- We need a reliable way to assess risk:
  - We want to see whether risk-assessment improves the selection of patients
  - We want to compare how effective risk-assessment is when done by clinicians vs. when done by a mathematical model: SepsisFinder

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Study Population

- 1414 blood cultures from patients eligible for a recent clinical trial at AUSL Romagna, samples drawn from patients presenting at the emergency department at 5 hospitals in the region
- Aim of the clinical trial was to assess the impact of Iridica PCR-ESI MS
- Clinicians were instructed to order samples for Iridica in addition to BC for those meeting Sepsis-3 criteria for sepsis/septic shock
- Data includes results for 1414 blood cultures and 275 Iridica samples

- Exclusion for the risk-assessment study:
  - Two or fewer “infection variables”
  - BC results missing

- Final dataset: 1264 blood cultures, 244 of which were associated with concurrent Iridica samples

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Study Population

N patients	1193
Age, median [IQR]	72 [55-82]
N blood cultures	1264
N positive	408
N considered significant*	332 (390 isolates)
Gram positive	117
Gram negative	270
Yeast/Fungi	3
Place of culture draw	
Ravenna	543 (43%)
Rimini	451 (36%)
Cesena	195 (15%)
Lugo	39 (3%)
Forli	36 (3%)

*Potentially underestimated – for this study all CoNS, *viridans* Streptococci, corynebacteria spp., bacillus spp. (except anthracis), propionibacterium spp., aerococcus spp. and micrococcus spp. were considered contaminants.

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Present study – Patient selection

- We wanted to assess how “good” the selection was

  → good selection is a high proportion of BC+ and/or Ir+

- We assume that selection of patients with a high proportion of significant positive blood cultures will also mean a high proportion of significant positive rapid diagnostic tests (where carried out)

Clinicians:

- 244 blood cultures with concurrent Iridica samples (selected prospectively)

SepsisFinder (model-based) selection:

- We developed a model that calculates the probability of bacteraemia
- We performed an independent, retrospective selection of the 244 blood cultures with the highest probability of bacteraemia

The model: SepsisFinder (SF)

- We use a causal probabilistic network to describe a partial model of the systemic inflammatory response
- Observed/input variables are commonly recorded parameters such as vitals, clinical chemistry, haematology
  - Temperature, chills, neutrophils, leukocytes, platelets, lactate, albumin, heart rate, mean arterial pressure, CRP, creatinine
- For the present study, we reduced the model to use only those variables we had access to:
  - Neutrophils, leukocytes, platelets, bilirubin, CRP
- The model was trained using 4707 cases of patients suspected of infection at Beilinson hospital in Israel from 2002-2016

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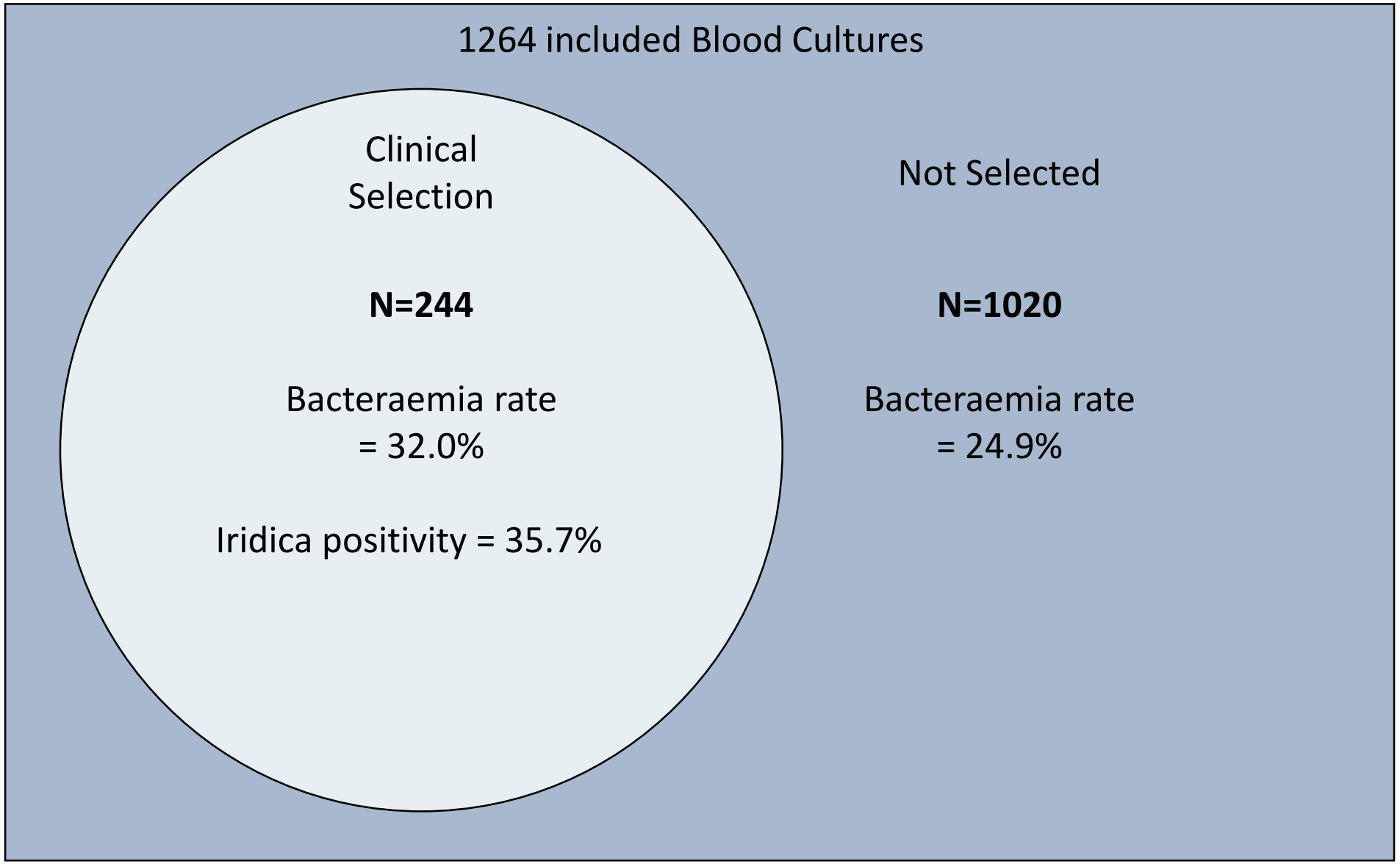
Patient Selection

Included Blood Cultures = 1264

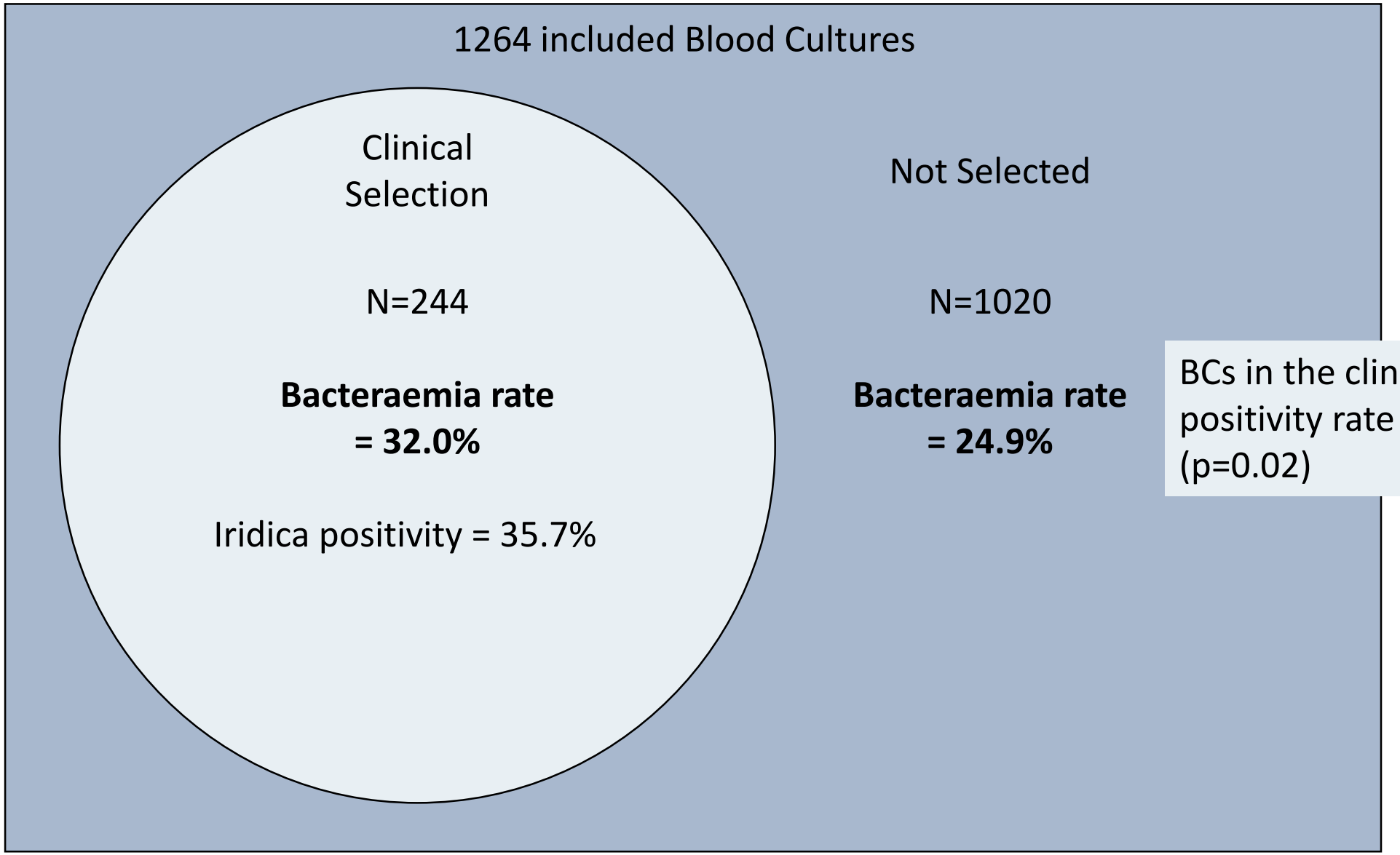
Positive BCs = 408 (32.3%)

Bacteraemia rate = 26.3%

Clinical Selection

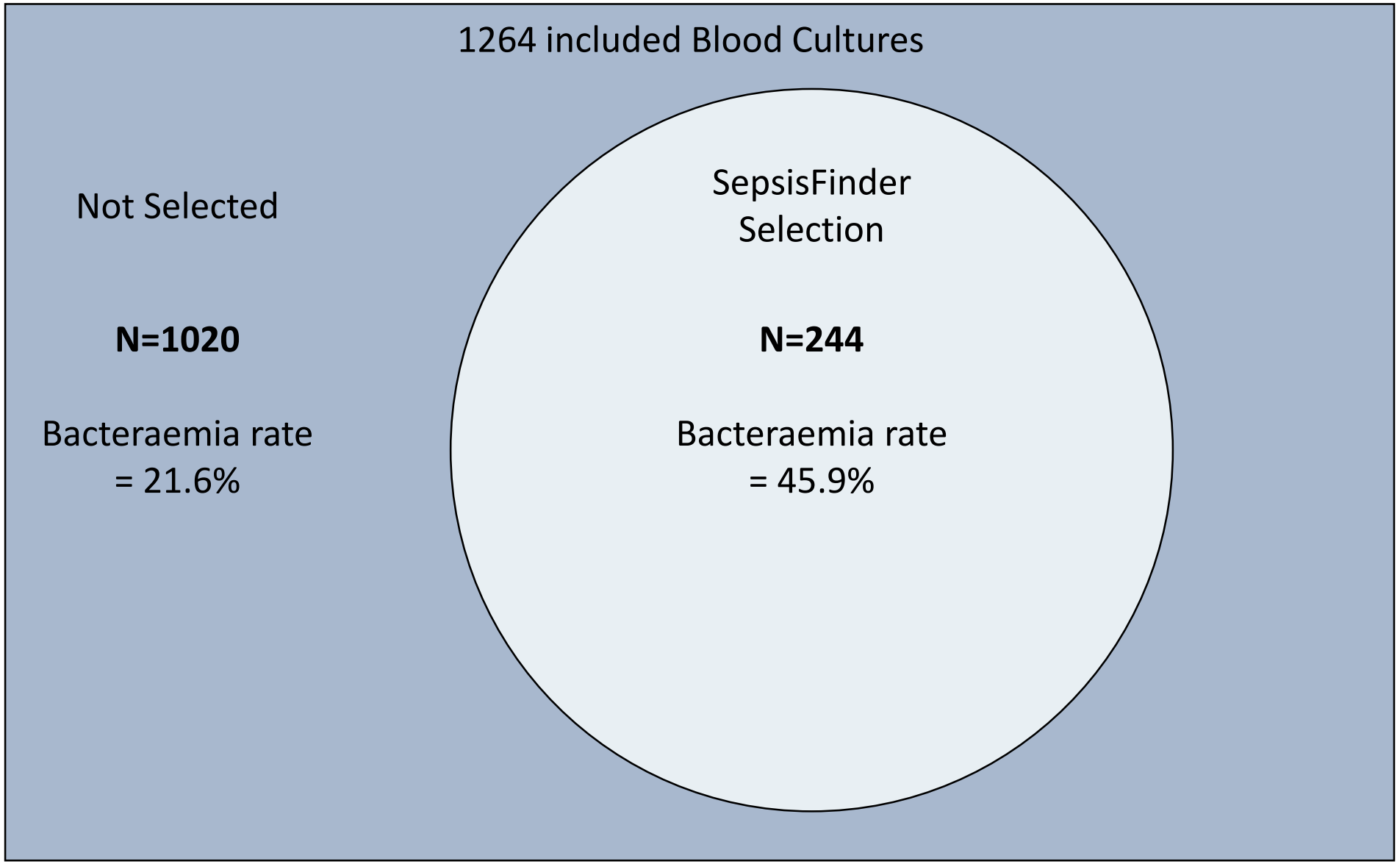


Clinical Selection

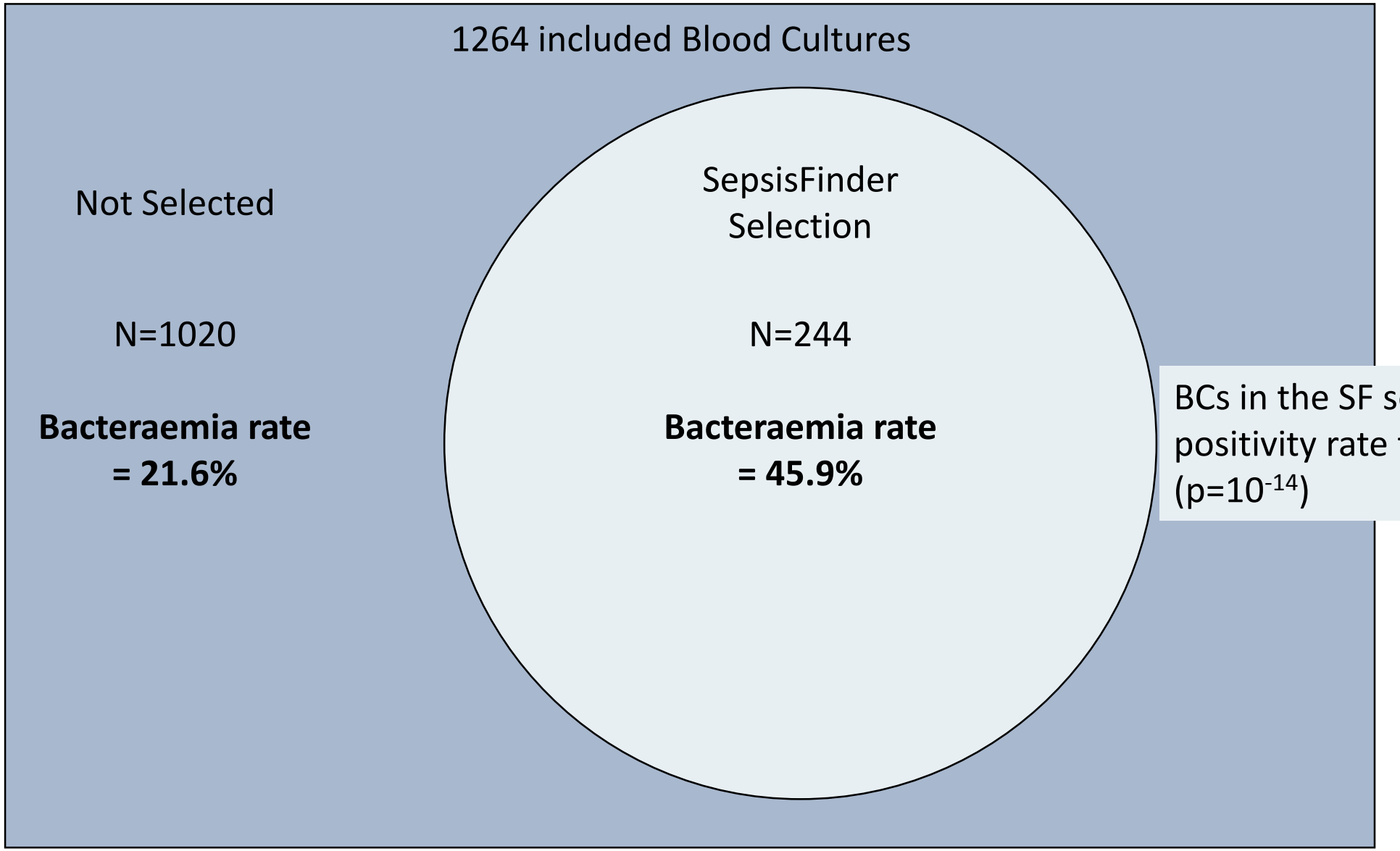


BCs in the clinician selection had a higher positivity rate than those not selected (p=0.02)

SF Selection

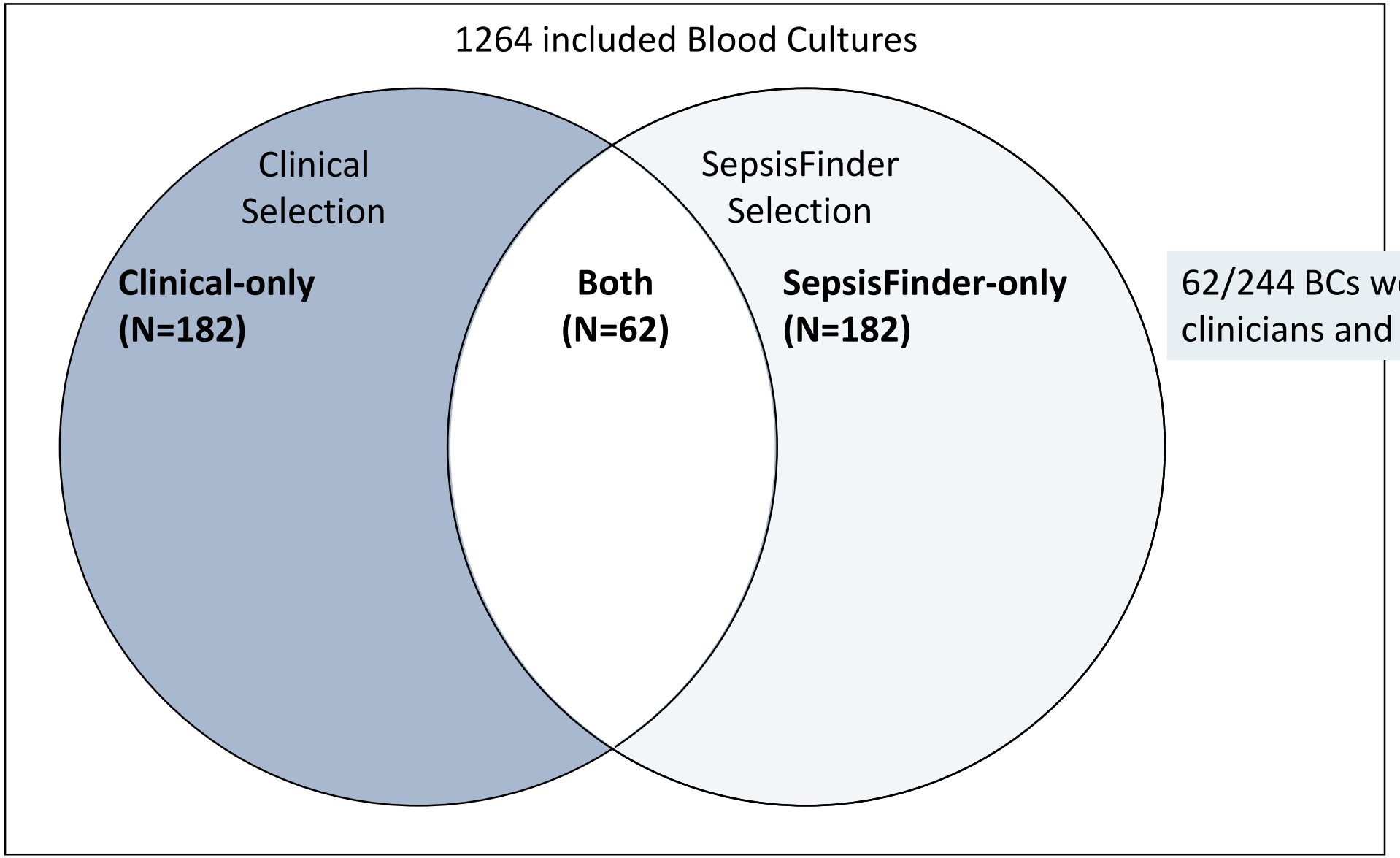


SF Selection



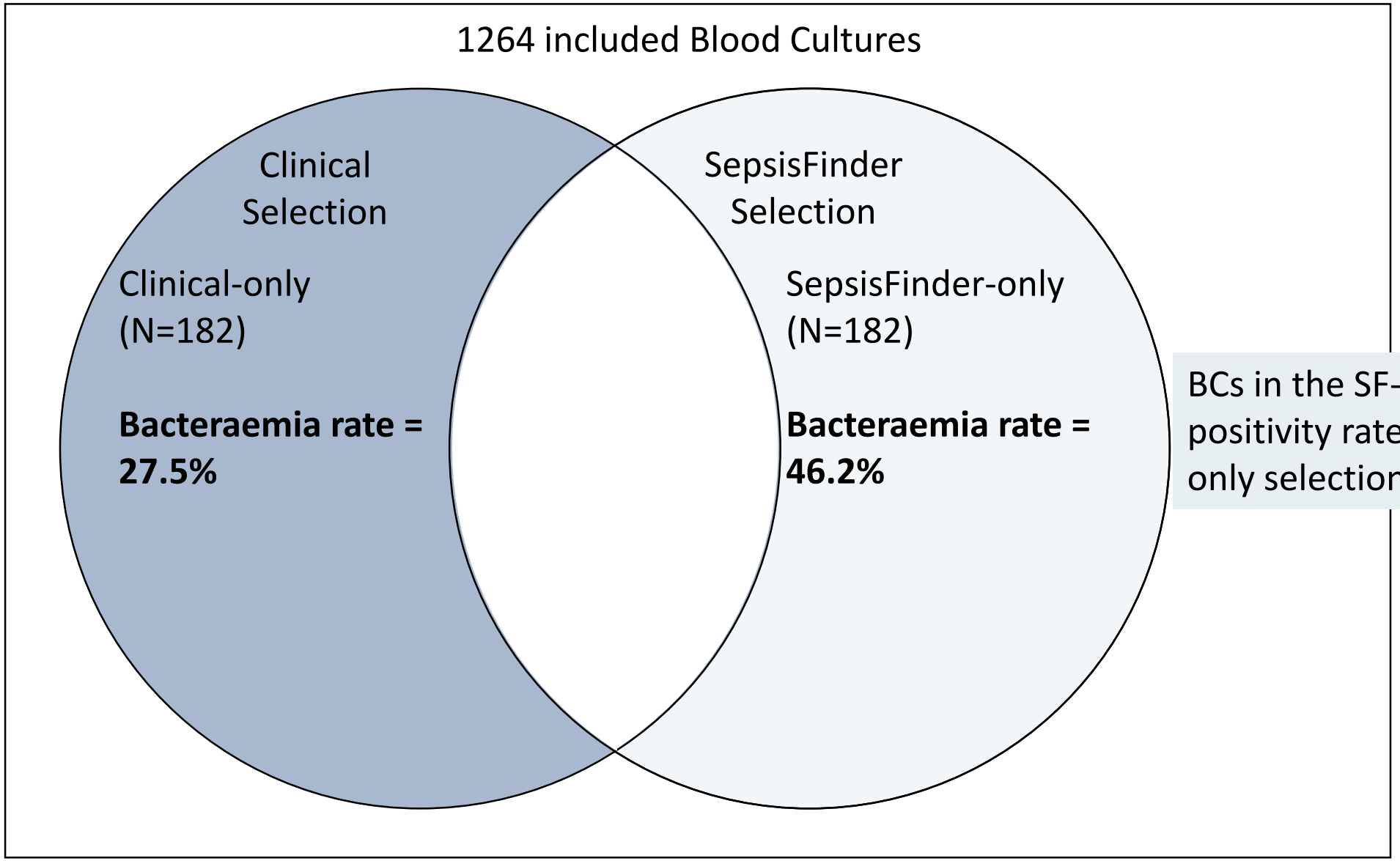
BCs in the SF selection had a higher positivity rate than those not selected ($p=10^{-14}$)

Clinical only vs. SF only



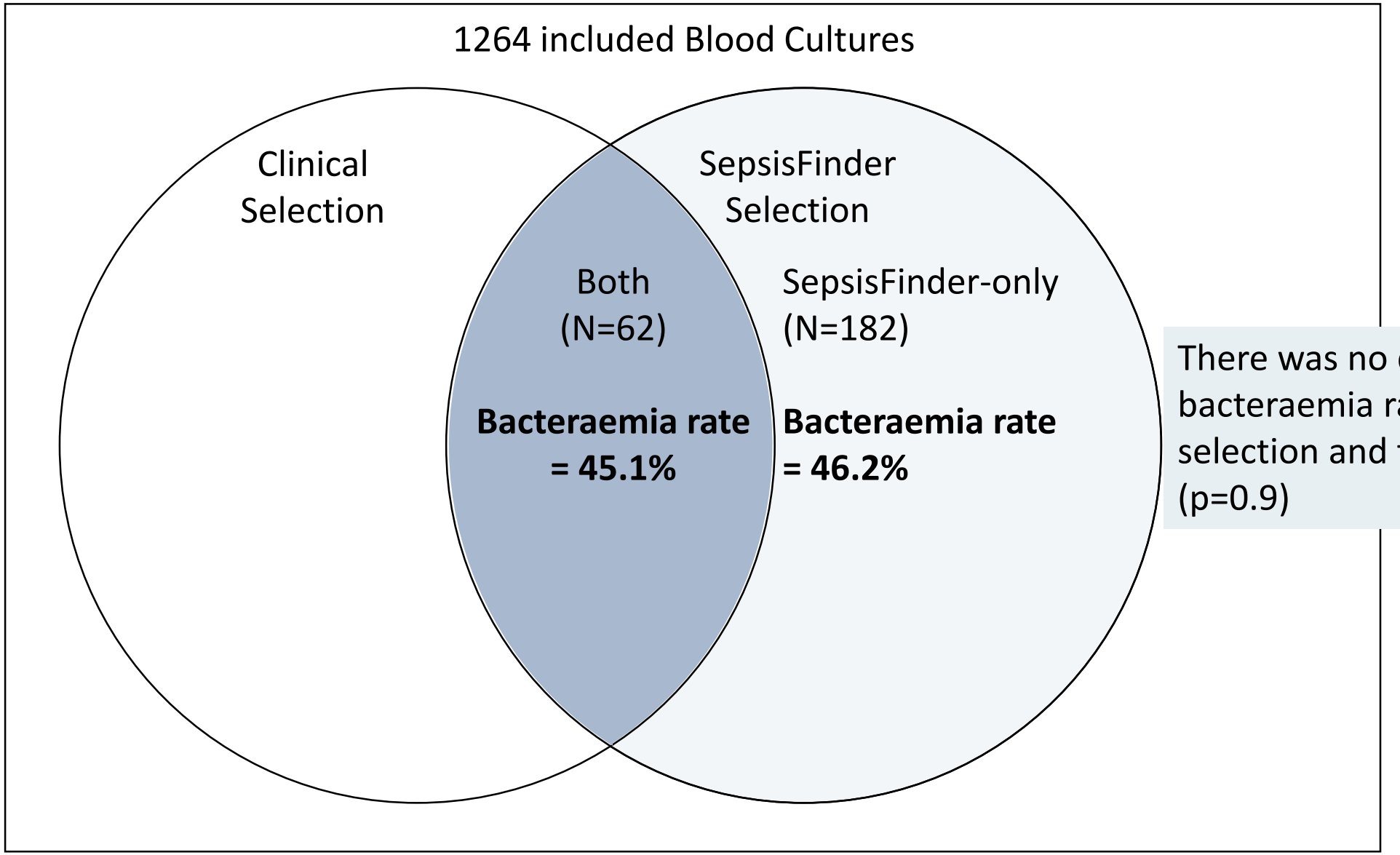
62/244 BCs were selected both by clinicians and by SF

Clinical only vs. SF only



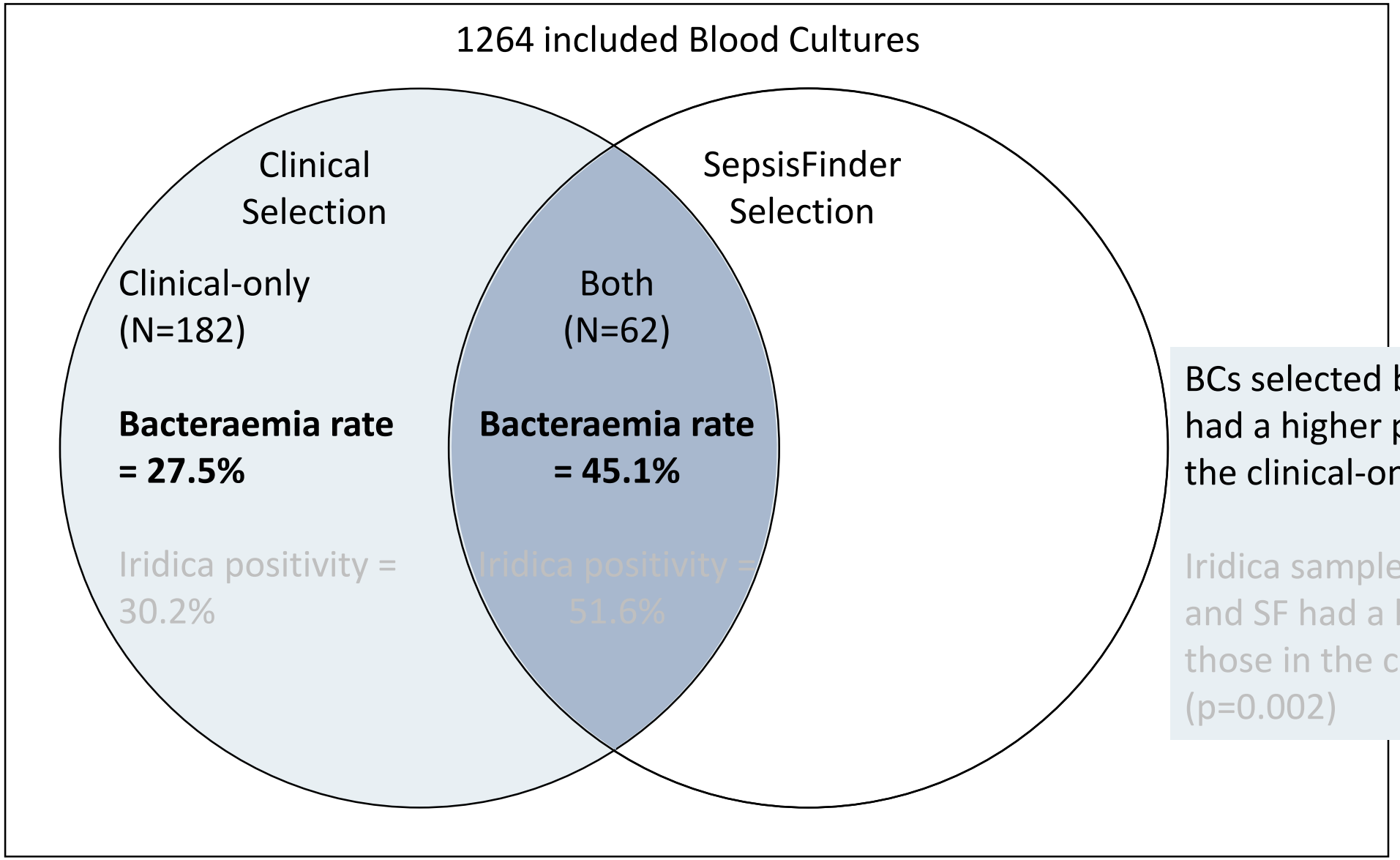
BCs in the SF-only selection had a higher positivity rate than those in the clinical-only selection (p=0.002)

Both vs. SF only



There was no difference between the bacteraemia rate in the BCs in the SF-only selection and those in selected by both (p=0.9)

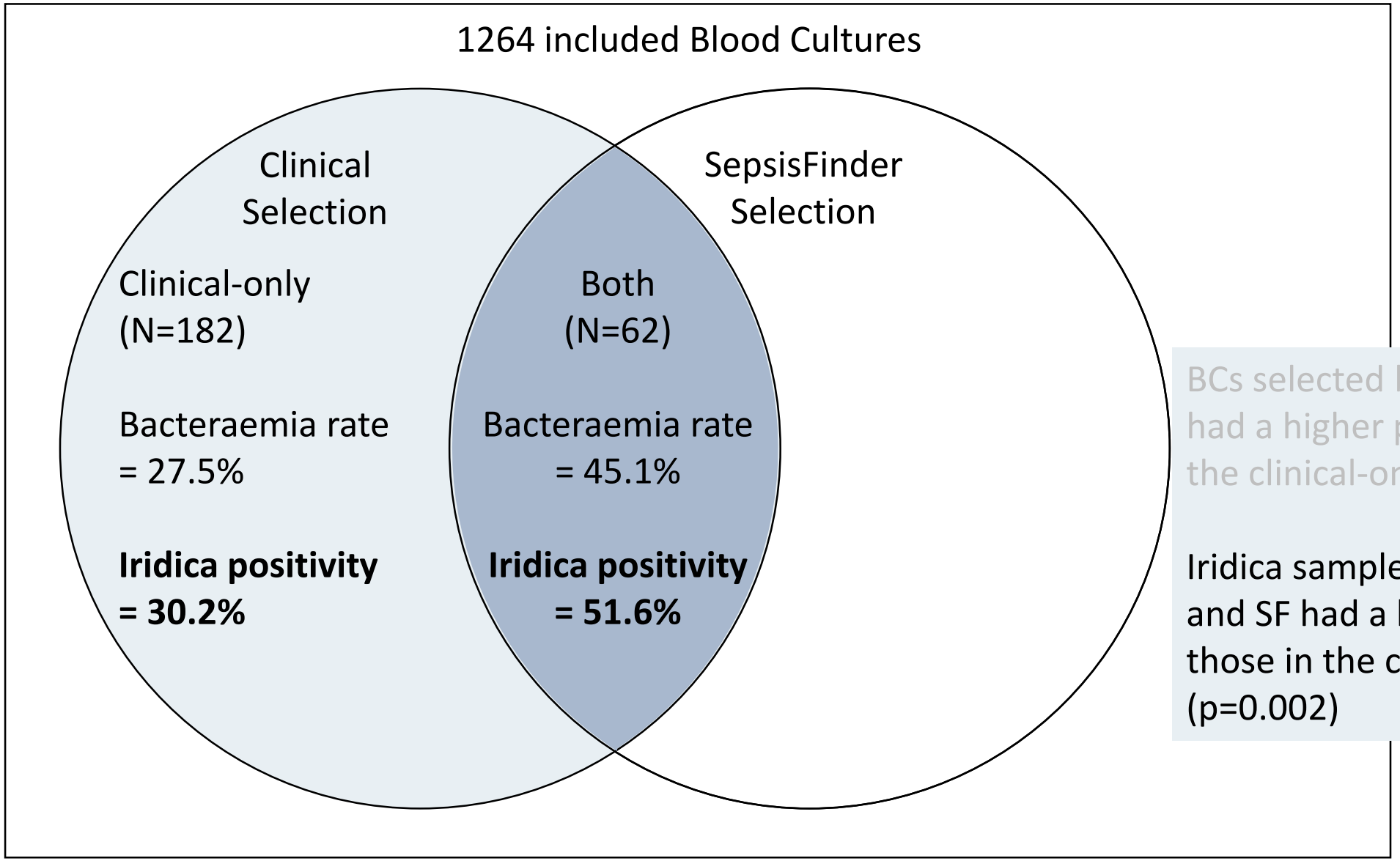
Both vs. Clinical only



BCs selected both by clinicians and SF had a higher positivity rate than those in the clinical-only selection (p=0.01)

Iridica samples selected both by clinicians and SF had a higher positivity rate than those in the clinical-only selection (p=0.002)

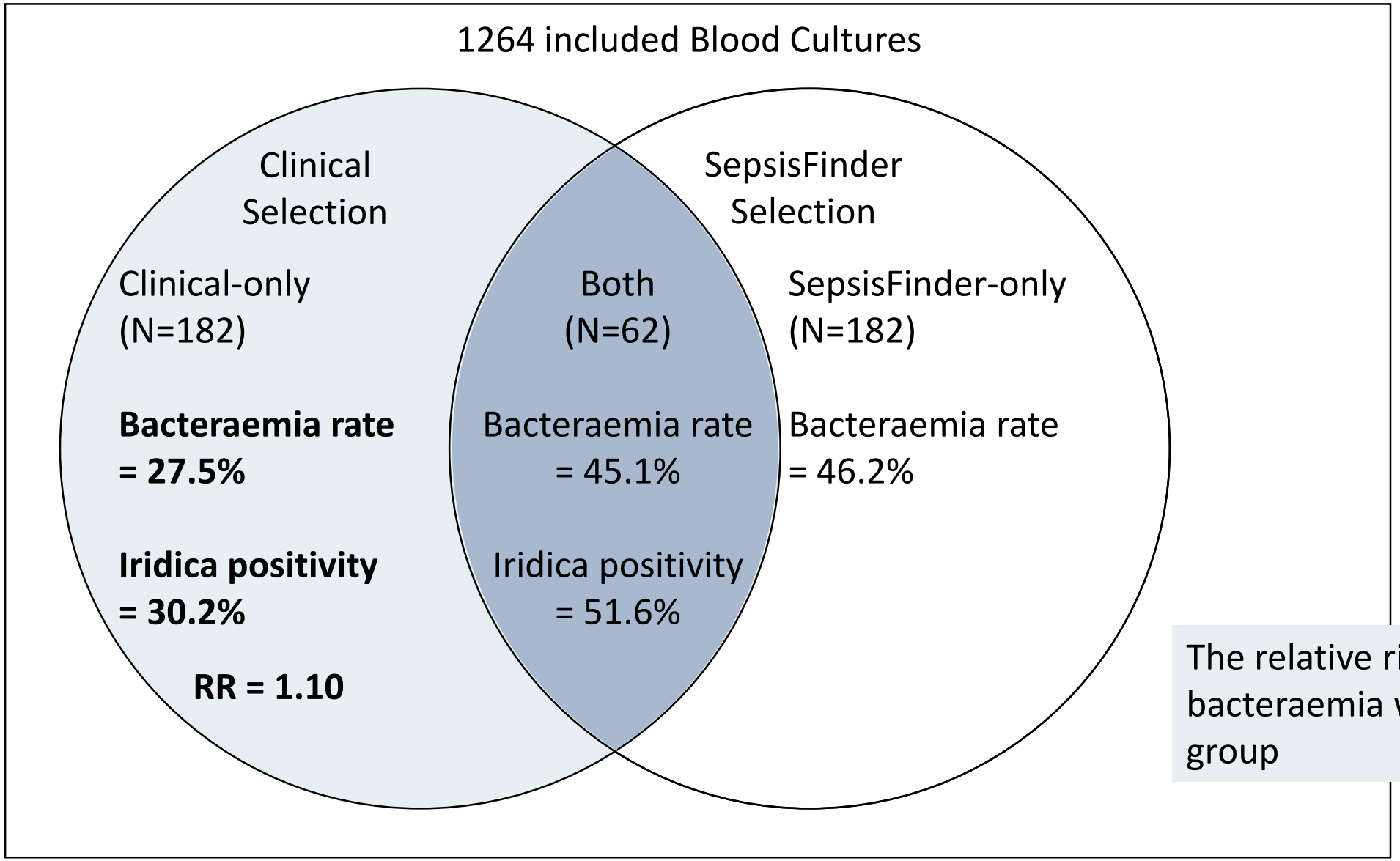
Both vs. Clinical only



BCs selected both by clinicians and SF had a higher positivity rate than those in the clinical-only selection (p=0.01)

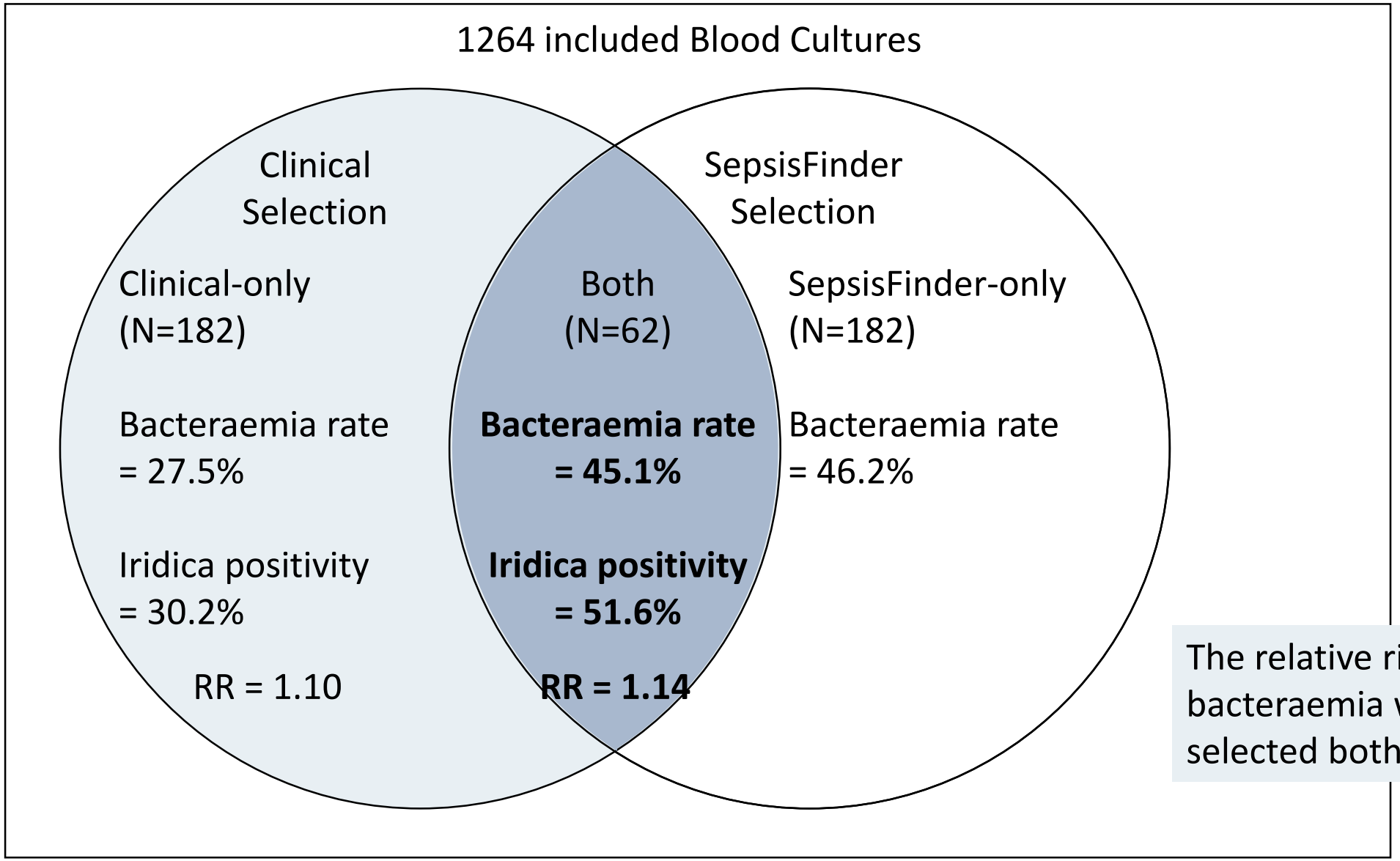
Iridica samples selected both by clinicians and SF had a higher positivity rate than those in the clinical-only selection (p=0.002)

Relative Risk – Iridica/Bacteraemia



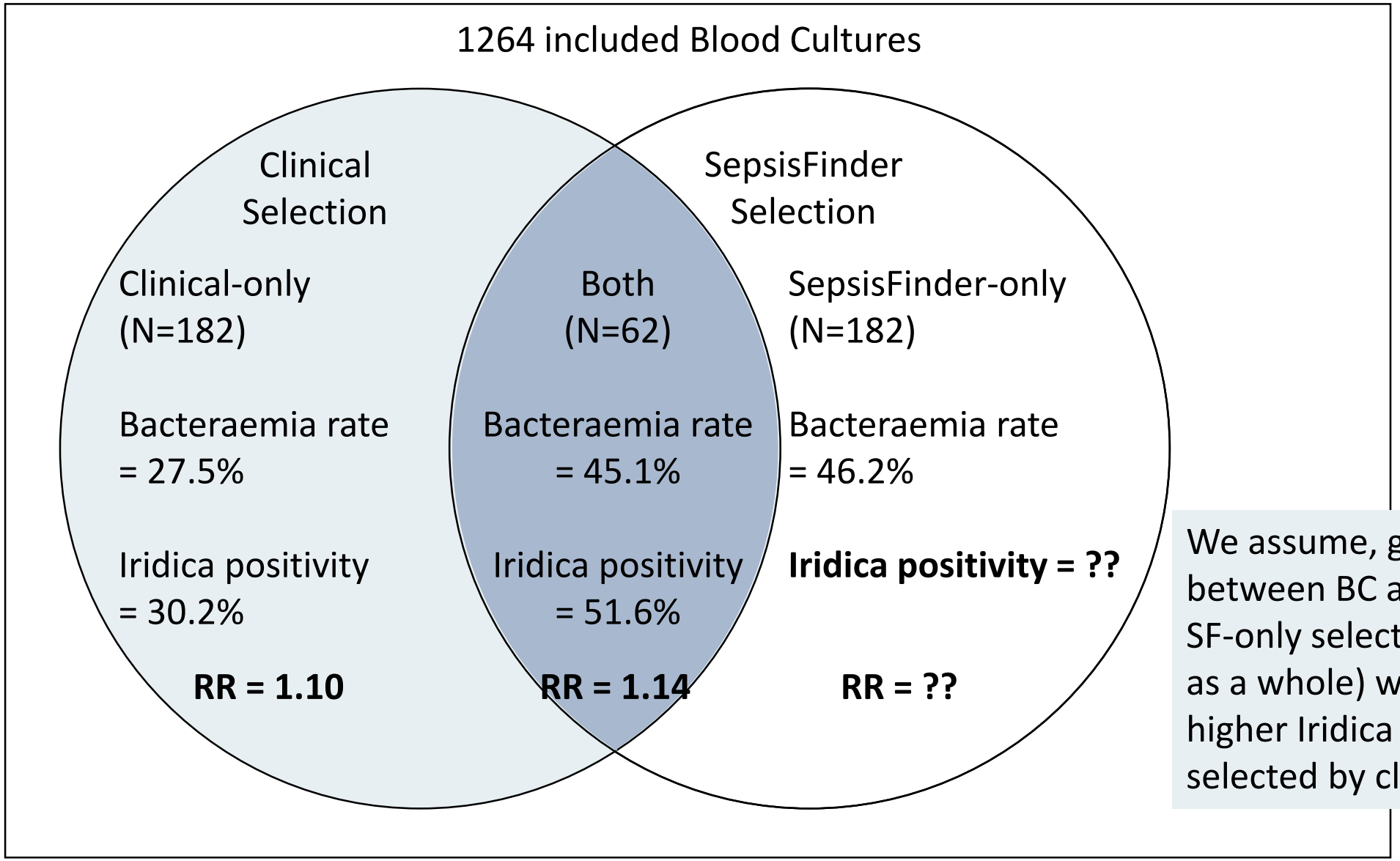
The relative risk for Iridica positivity vs. bacteraemia was 1.10 in the clinical only group

Relative Risk – Iridica/Bacteraemia



The relative risk for Iridica positivity vs. bacteraemia was 1.14 in the group selected both by clinicians and SF

Relative Risk – Iridica/Bacteraemia



We assume, given the correlation between BC and Iridica positivity, that the SF-only selection (and thus SF selection as a whole) would have a significantly higher Iridica positivity rate than those selected by clinicians

Analysis – Potential impact

- No data on 30-day mortality (yet) for the present dataset, but…

(Mostly) independent cohort from the same setting:

- 3202 BCs from January 1 2015 – June 30 2016 (1063 (33%) BC+, 744 (23%) bacteraemia)
- 30-day mortality was 13%
- AUC (bacteraemia) was 0.74
- Selecting the 20% with highest probability of bacteraemia gave a rate of 48%
- Among these, 30-day mortality was 23% (25% for those with bacteraemia)

We can assume that for the present dataset, the SF high-risk group had a higher mortality rate than those not selected → this is a high-risk group

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Summary

Key findings:

- SF's high-risk group had a significantly higher rate of bacteraemia
- Of the clinical selection, both the rate of bacteraemia and positive Iridica samples were higher among those that were also selected by SF

Conclusions:

- **SepsisFinder improved patient selection for rapid diagnostic testing by "enriching" the test population**
- **SepsisFinder's risk assessment was more effective than clinicians**

However:

- This work is ongoing and we still need to investigate the other side of "good" selection:
  - Does a higher test positivity rate lead to earlier covering treatment?
  - Does it reduce mortality?

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