U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Numbers:	50-679
Drug Name:	Maxipime (cefepime hydrochloride)
Indication(s):	Pneumonia Febrile neutropenia Uncomplicated and complicated urinary tract infections Uncomplicated skin and skin structure infections Complicated intra-abdominal infections
Applicant:	Bristol-Myers Squibb
Submission Date:	August 8, 2008
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Keywords: Meta-analysis, mortality risk

[SEE ADDENDUM ATTACHED TO THIS REVIEW]

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The purpose of this review is to assess whether cefepime is associated with an excess risk of mortality versus comparator drugs. This meta-analysis is based on both trial-level and patient-level data from clinical trials for which data were available to the sponsor, Bristol-Myers Squibb. Eighty-eight randomized, placebo or active-controlled studies (cefepime: 9467; comparator: 8288) are included in the trial-level analysis, and thirty-five randomized, placebo or active-controlled studies (cefepime: 5058, comparator: 3976) are available in the patient-level analysis. The primary endpoint is 30-day all-cause mortality.

A meta-analysis published in the Lancet Infect Dis by Yahav (2007) analysis was based on 41 studies which comprised a subset of our trial-level data, but not patient-level data. The conclusions of significantly higher mortality rate in the cefepime group compared to the comparator group (risk ratio: 1.26; 95% CI: 1.08-1.49) as reported in Yahav's paper was not confirmed in the FDA analysis. The FDA analysis was based on a broader spectrum of data sources and found that the mortality risk difference in the cefepime group was greater, but this increase was not found to be statistically significant in both trial-level and patient-level analyses.

Subgroup analyses were conducted, most of which did not demonstrate a significantly increased mortality associated with cefepime treatment. However, significantly greater mortality was demonstrated for cefepime-treated patients in the following subgroups: patients treated for the indication of skin and skin structure infections, patients with baseline pathogens resistant to study therapy, and patients with febrile neutropenia with solid tumors at baseline. The numbers of subjects available in these subgroups were very small, thus resulting in wide confidence intervals. Therefore, significant findings from these subgroups need to be re-examined when more data are available.

1.2 Brief Overview of Clinical Studies

Cefepime hydrochloride was approved in the United States in 1996. The approved indications include pneumonia, empiric therapy for febrile neutropenic patients, uncomplicated and complicated urinary tract infections, uncomplicated skin and skin structure infections, and complicated intra-abdominal infections. Safety concern about the potential for elevated risk of mortality associated with cefepime use was raised by a published meta-analysis by Yahav et al[1] (2007). To explore this possible association, we asked the sponsor to submit all available clinical trial data to re-examine the potential elevated mortality risk associated with cefepime. FDA pre-specified the statistical analysis plan for the meta-analysis including the definitions of the endpoints, study populations, subgroups, and statistical methods.

1.3 Statistical Findings

In the overall analysis, both trial-level and patient-level analyses gave similar conclusions that cefepime was associated with greater mortality risk compared to comparator, however, this difference was not found to be statistically significant. The risk difference estimate for the trial-level analysis was 5.38 per 1000 population (95% CI: (-1.53, 12.28)), and for the patient-level analysis was 4.83 per 1000 population (95% CI: (-4.72, 14.38)).

In the subgroup analysis, there was no significant effect for most factors we examined, except for the indication of skin structure infections [RD estimate: 17.97 per 1000 population, 95% CI: (3.73, 32.21)], patients with pathogens isolated at baseline resistant to study therapy [RD estimate: 67.47 per 1000 population, 95% CI: (16.30, 118.61)] and febrile neutropenia patients with solid tumor at baseline[RD estimate: 69.74 per 1000 population, 95% CI: (8.13, 131.35)]. Patients with febrile neutropenia, pneumonia and skin structure infections receiving cefepime had greater mortality risk compared to those receiving comparator drugs. Patients taking cefepime had greater mortality risk compared to those taking ceftazidime and piperacillin-tazobactam. The risk difference estimates for patients aged ≥ 18 years old were greater than 0. Caucasians comprised 65% of the study population and were the only subgroup with risk difference greater than 0, besides Asians. However, Asians comprised only 0.25% of study population so that the confidence interval was very wide. Both US and non-US populations had positive risk difference but the estimate in the non-US population was notably larger.

Several sensitivity analyses were performed to examine the robustness of the primary results to the inclusion of small trials, to microbiological ITT population, and to statistical methods. The inclusion of small trials did not substantially affect the overall estimate. All analyses in the microbiological ITT population showed findings consistent with the primary results from the safety ITT population. Various statistical methods also gave similar findings as did our primary analysis method.

2. INTRODUCTION

2.1 Background

Cefepime hydrochloride has been approved in the United States since 1996. The approved indications include pneumonia (moderate to severe caused by Streptococcus pneumoniae, including cases associated with concurrent bacteremia, Pseudomonas aeruginosa, Klebsiella pneumoniae, or Enterobacter species), empiric therapy for febrile neutropenic patients, uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, and complicated intra-abdominal infections. The dosing regimens vary from 0.5 – 2 gram every 8-12 hours, depending on the indication. Also, it is approved for use in the pediatric population 2 months of age and older.

The Food and Drug Administration (FDA) became concerned about the potential for elevated risk of mortality with cefepime after Yahav et al (2007) published a meta-analysis entitled, "Efficacy and safety of cefepime: a systematic review and meta-analysis", in Lancet Infect Dis. that showed a higher all-cause mortality in cefepime-treated patients as compared to patients treated with other β-lactam antibiotics (risk ratio = 1.26 with 95% confidence interval [1.08-1.49]). The difference in all-cause mortality was also significant for the febrile neutropenia subgroup (risk ratio = 1.42 with 95% CI [1.09-1.84]). The analysis was based on 41 randomized trials that compared cefepime with another β-lactam antibiotic alone or with the addition of a non-β-lactam antibiotic to both study groups.

In July 2007, FDA requested the sponsor, Bristol-Myers Squibb (BMS), to provide interpretation and comments regarding Yahav et al's findings. Subsequent letters in August, November and December 2007, and January and March 2008 were sent to BMS to request additional information. Additional letters in April and May 2008 requested the trial-level summaries and patient-level data for this review.

Prior to the analysis of the cefepime data, medical reviewers in the Division of Anti-infective and Ophthalmology Drug Products and statistical and medical reviewers in the Quantitative Safety and

Pharmacoepidemiology Group agreed upon the definition of the research objectives, endpoints, study populations, and subgroups to be examined; and the specification of the statistical methods. These elements were incorporated into a statistical analysis plan prior to the review.

2.2 Objectives

1. Examine if cefepime use is associated with an increased risk of mortality relative to the use of comparator drugs in randomized controlled trials.
2. Examine if the risk of mortality varies by (a) indication, (b) comparator drug or drug groups, (c) baseline risk factor subgroups, and d) demographic subgroups.

2.3 Data Sources

2.3.1 Data Requests

In April and May 2008, FDA sent letters to the sponsor requesting both the trial-level summaries and patient-level data to assess the possible association between the use of cefepime and all-cause mortality. The trial-level summaries include patient and mortality counts, indication, and comparator drug(s). The inclusion criteria for studies included in the trial-level summaries are as follows:

1. Fifty-seven studies as cited in the paper by Yahav
2. All parallel-arm, randomized, controlled trials conducted with cefepime
3. Trials in which cefepime was administered as randomized treatment, either with or without adjunct therapy
4. Placebo- and/or active-controlled trials
5. All U.S. and non-U.S. trials available including those not previously submitted to the FDA
6. Studies with at least 10 subjects per treatment arm included

The patient-level datasets include variables for patient and trial identification, demographics, disposition, mortality information, and risk factor information. In conjunction with the patient-level dataset, a detailed trial-level dataset was requested that summarizes and characterizes the trials. This information includes indications, study duration, number of subjects per treatment group, dosage, and design features. The inclusion criteria for studies included in the patient-level dataset were as follow:

1. All parallel-arm, randomized, controlled trials conducted with cefepime
2. Trials in which cefepime was administered as randomized treatment, either with or without adjunctive therapy
3. Placebo- and/or active-controlled trials
4. All U.S. and non-U.S. trials available including those not previously submitted to the FDA
5. Studies with at least 10 subjects per treatment arm included

The flow diagrams showing the process of selecting studies to include in trial-level and patient-level analyses are shown in Figures 1 and 2. A listing of the trials, the treatment groups, patient and mortality counts are also included in Appendix I.

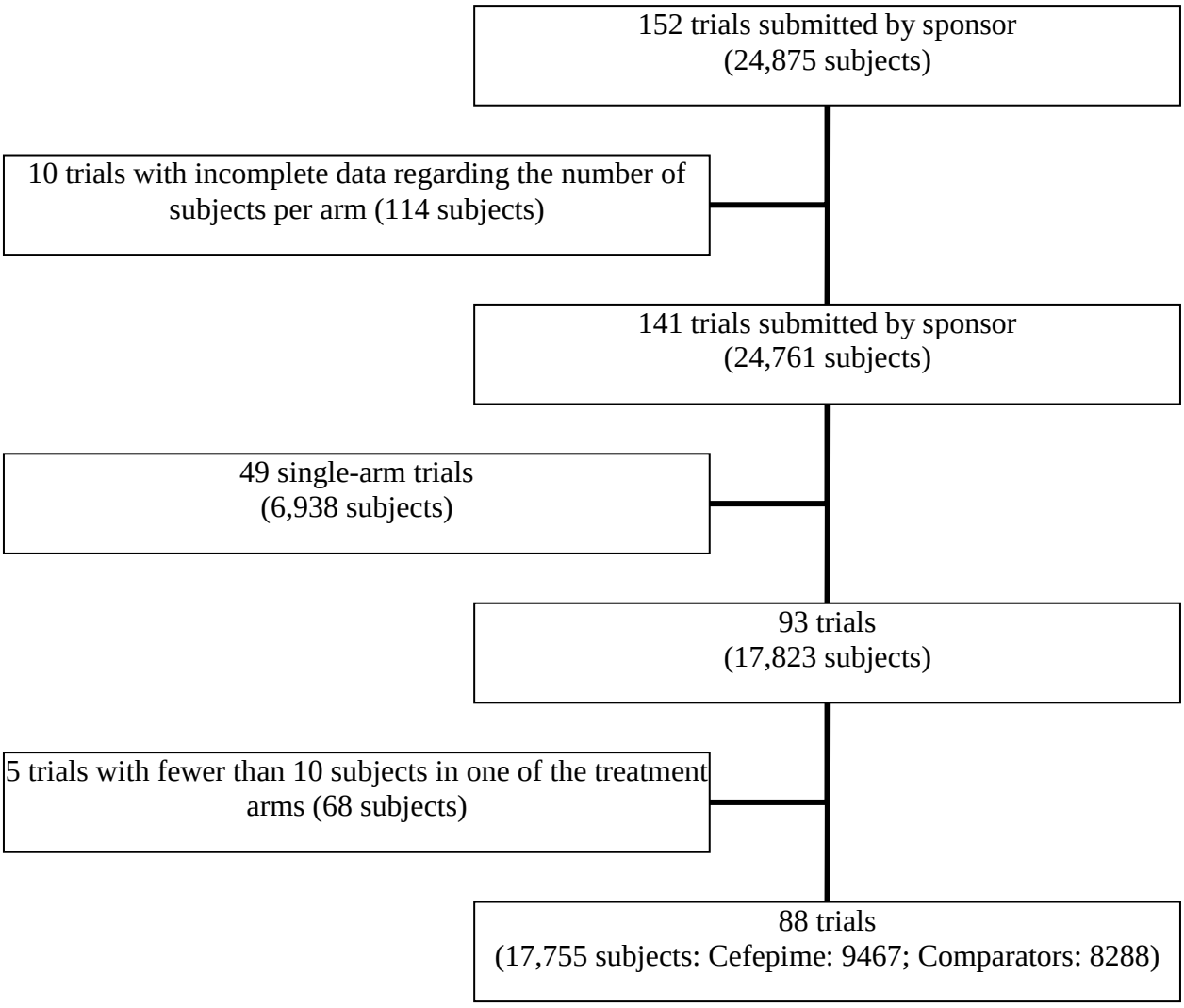


Figure 1: Flow diagram for trial-level analysis

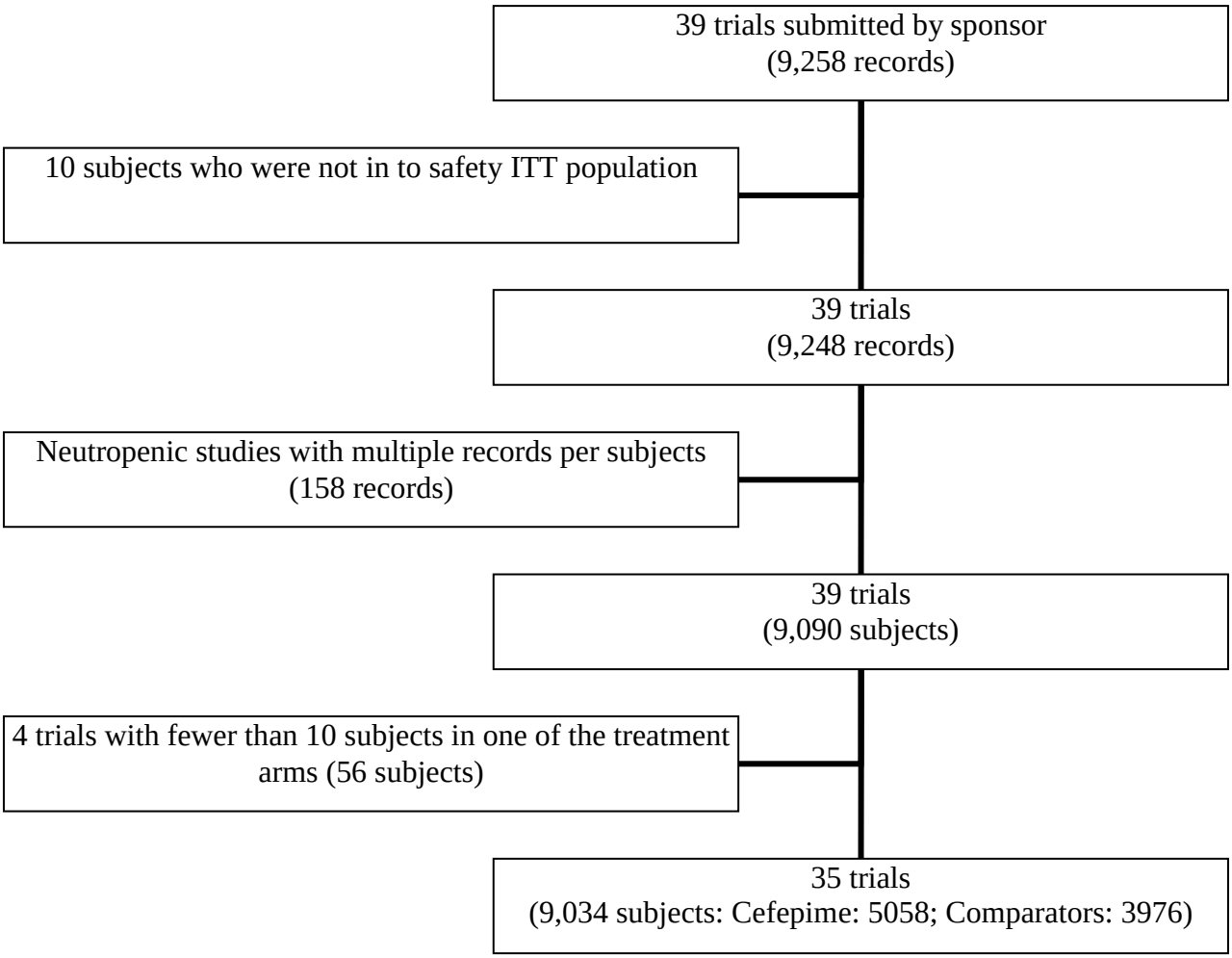


Figure 2: Flow diagram for patient-level analysis

2.3.2 Summaries of the Study Data

2.3.2.1 Trial-level Data

Eighty-eight randomized, comparative studies were available for the trial-level analysis with a total of 9467 subjects in the cefepime arms and 8288 subjects in the comparator arms. Tables 1 and 2 show the number of trials and number of subjects in the treatment group by indication and comparator drug. Indications were categorized by the approved indications. Febrile neutropenia and pneumonia were the indications with the largest number of subjects in the study comprising 30.69% and 22.80% of the study population, respectively. More than half of the study population was included in the trials with ceftazidime as the comparator drug.

Table 1: Trials by Indication in the Trial-level Data

Indications	Number of Studies	Number of subjects	
		Cefepime (%)	Comparator (%)
Febrile Neutropenia	24	2791(29.48)	2658(32.07)
Intra-abdominal Infection	7	628(6.63)	470(5.67)
Pneumonia	26	2228(23.53)	1821(21.97)
Urinary Tract Infection	7	763(8.06)	490(5.91)
Skin Structure Infection	2	335(3.54)	165(1.99)
Other	22	2722(28.75)	2684(32.38)
Total	88	9467	8288

Table 2: Trials by Comparator Drug in the Trial-level Data

Type of Comparator Drug	Number of Studies	Number of subjects	
		Cefepime (%)	Comparator (%)
Ceftazidime	47	5430(57.36)	4580(55.26)
Piperacillin-tazobactam	6	965(10.19)	976(11.78)
Imipenem-meropenem	6	782(8.26)	749(9.04)
Ceftriaxone-cefotaxime	17	1270(13.42)	1140(13.75)
Other	11	818(8.64)	641(7.73)
Mixed treatment	1	202(2.13)	202(2.44)
Total	88	9467	8288

2.3.2.2 Patient-level Data

Thirty-five randomized, comparative studies were available for the patient-level analysis with a total of 5058 subjects in cefepime arm and 3976 subjects in comparator arm. Tables 3 and 4 show the number of trials and number of subjects in the treatment group by indication and comparator drug. Indications were categorized by the approved indication. Patients with febrile neutropenia, intra-abdominal infection and pneumonia were the largest groups in the study comprising 15.52% and 11.14% and 10.13% of the study population, respectively. More than 70 percent of the study population was included in the trials with ceftazidime as the comparator drug. Patients in study 411132 took either ceftazidime or ceftriaxone as the comparator drug. Therefore, this study was counted twice in the total number of studies.

Table 3: Trials by Indication in the Patient-level Data

Indications	Number of Studies	Number of subjects	
		Cefepime (%)	Comparator (%)
Febrile Neutropenia	7	776(15.34)	626(15.74)
Intra-abdominal Infection	5	585(11.57)	421(10.59)
Pneumonia	4	609(12.04)	306(7.70)
Urinary Tract Infection	4	426(8.42)	242(6.09)
Skin Structure Infection	2	335(6.62)	165(4.15)
Other	13	2327(46.01)	2216(55.73)
Total	35	5058	3976

Table 4: Trials by Comparator Drug in the Patient-level Data

Type of Comparator Drug	Number of Studies	Number of subjects	
		Cefepime (%)	Comparator (%)
Ceftazidime	21	3617(71.51)	2839(71.40)
Piperacillin-tazobactam	1	59(1.17)	57(1.43)
Imipenem-meropenem	1	164(3.24)	159(4.00)
Ceftriaxone-cefotaxime	9	794(15.70)	654(16.45)
Other	4	424(8.38)	267(6.72)
Total	36	5058	3976

3. Statistical Evaluation of Safety

The statistical analysis plan (SAP) including the definitions of the endpoints, study population, subgroups, and statistical methods were pre-specified prior to conducting the review. Medical Officers from the Division of Anti-infective and Ophthalmology Products and QSPG reviewed and provided comments which were incorporated into the final SAP. Deviations from the SAP are noted.

3.1 Study endpoint and analysis population

The primary endpoint is 30-day post-therapy all-cause mortality.

For the trial-level meta-analysis, the primary analysis population is the intent-to-treat (ITT) population which is defined as all patients randomized. The ITT population is chosen as the primary population for being able to include all available trial-level data in the analysis, given that limited information is available for some studies from publications or conference abstract.

For the patient-level meta-analysis, the primary analysis population is the safety intent-to-treat (SITT) population which is defined as all patients who received at least one dose of study drug and patient status known at any time after start of study drug.

The secondary analysis population is microbiological ITT population which is defined as all patients who received at least one dose of study drug and also had a bacterial pathogen cultured at baseline.

3.2 Subgroups

The following subgroups were analyzed for patient-level data. For the trial-level meta-analysis, only indication and comparator drug were analyzed.

3.2.1 Indications Pursued

Five indications were considered.

1. Pneumonia
2. Febrile neutropenia
3. Urinary tract infections
4. Skin structure infections
5. Intra-abdominal infections
6. Other

3.2.2 Comparator Drugs

Four comparator antibiotics were included: ceftazidime, piperacillin-tazobactam, imipenem-meropenem, ceftriaxone-cefotaxime and other (patients took comparator antibiotics other than the ones in the pre-specified groups).

3.2.3 Demographics

The following subgroup classes were considered:

1. Age: Age-groups (0 to < 18, 18 to < 55, 55 to < 65, and 65 and above).
2. Gender
3. Race: Caucasian, Hispanic, Black or African American, Asian/Pacific islanders, and Other
4. Region: United States or Rest-of-the world (ROW)

3.2.4 Risk Factors

The following subgroups of special interest were considered:

1. Any pathogen recovered at baseline: Yes, No
2. All pathogens isolated at baseline are susceptible to study therapy: Yes, No

3.2.5 Other (Post-hoc) Risk Factors

The following subgroup classes were also considered:

1. Fungal pathogen recovered at baseline: Yes, No
2. Baseline infection: Mono-microbial, Poly-microbial
3. Renal insufficiency or failure at baseline: Yes, No
4. Active cancer or malignancy at baseline (febrile neutropenic patients only): Solid tumor, Hematologic malignancy
5. Bone marrow transplant at baseline (febrile neutropenic patients only): Yes, No

3.3 Statistical Methods

3.3.1 Primary Method

The primary analysis method described in the SAP was the Mantel-Haenszel risk difference[2]. Upon receiving the data, the statistical reviewer changed the primary method from the exact odds ratio to Mantel-Haenszel risk difference due to the number of trials with no event in both treatment groups. The risk difference method is able to include trials with zero events in both arms into the analysis while exact odds ratio method excludes those trials in the stratified analysis. The unit of analysis was the subject and the stratification factor was the trial.

3.3.2 Sensitivity Methods

Exact method for a stratified odds ratio[3] and 95% confidence interval (Agresti 1992) was used for the sensitivity analysis. The odds ratio was in terms of patient units. The stratification factor was the trial.

Zelen's test was used to test the hypothesis of a common odds ratio across trials. A random-effect meta-analysis based on the Mantel-Haenszel odds ratio was used to examine the effect of trial heterogeneity.

The point estimates and the 95% confidence intervals from the fixed-effect and random effect models were qualitatively compared.

3.3.3 Additional Methods for Patient-Level Meta-Analysis

Additional sensitivity analyses were performed on the patient-level data. Stratified risk ratio and 95% confidence interval using person-time units and a Cox proportional hazards model stratified by trial was employed to examine the consequences of the possibility of non-constant hazards and/or differential follow-up between the treatment arms.

3.3.4 Exploratory Patient-level analyses

3.3.4.1 Time Pattern

Kaplan-Meier survival curves were used to qualitatively examine the time-pattern (hazard function) of events.

3.3.4.2 Duration and Discontinuation

Differences in treatment arms within trials of treatment duration and premature discontinuation of patients were examined.

3.3.5 Missing Values

For each analysis, all patients with the necessary information for the specific analysis were used.

3.3.6 Multiplicity

Because the analysis was exploratory in nature, no adjustment for multiplicity was made.

3.3.7 Statistical Significance

Statistical significance refers to a two-sided type 1 error of 0.05.

4 Results

4.1 Patient Demographic and Baseline Characteristics

For both trial-level and patient-level data, number of trials and number of subjects in each treatment arm by indication and comparator drug are summarized in Section 2.3.2.

4.1.1 Patient-level Data

Age, sex, race and study location of the study population by treatment group are shown in Table 5. Patients in cefepime and comparator arms were balanced with respect to age, sex, race and study location with p-value greater than 0.05. The least-square means for age was 49 for both treatment groups. 40% of the patients were between ages 18-54 and 33% of the patients were aged 65 or older. 55% of the patients were male. A large majority of the patients were Caucasians (65%); Asians comprised only 0.25% of the study population. A large majority of the patients were in the US (65%).

Table 5: Baseline demographic characteristics

Demographic characteristics		Cefepime N = 5058 N (%)	Comparator N = 3976 N (%)	Total (N = 9034) N (%)
Age	0 – 17	474 (9.37)	448 (11.27)	922 (10.21)
	18 – 54	2114 (41.80)	1547 (38.91)	3661(40.52)
	55 – 64	820 (16.21)	597 (15.02)	1417(15.69)
	≥ 65	1650 (32.62)	1384 (34.81)	3034(33.58)
	Missing	0	0	0
	Mean[Std.]	49.32[23.64]	49.59[24.46]	49.44[24.00]
	Least-squares Mean	45.25	45.54	
	Range [Min-Max]	0.09 – 100	0.13 – 101	
Sex	Female	2299(45.45)	1772(44.57)	4071(45.06)
	Male	2759(54.55)	2204(55.43)	4963(54.94)
	Missing	0	0	0
Race	Asian	10(0.20)	13(0.33)	23(0.25)
	Black	727(14.37)	563(14.16)	1290(14.28)
	Hispanic	785(15.52)	595(14.96)	1380(15.28)
	White	3212(63.50)	2637(66.32)	5849(64.74)
	Other	45(0.89)	24(0.60)	69(0.76)
	Unknown	279(5.52)	144(3.62)	423(4.68)
Region	US	3299(65.22)	2593(65.22)	5892(65.22)
	Non-US	1759(34.78)	1383(34.78)	3142(34.78)

Table 6 displays the baseline study characteristics by treatment groups. For all factors examined, we can see the two treatment groups were homogenous. More subjects in the cefepime arm (43.81%) had pathogens isolated at baseline which were susceptible to study therapy compared to those in the comparator arm (39.91%). Table 7 shows the treatment discontinuation status and duration by treatment arm. Treatment discontinuation status were balanced between two treatment arms controlling for trial (p=0.0599). 72% of the patients discontinued early from the study therapy. Comparator patients (8.61 days) had a slightly larger least-squares mean for treatment duration than cefepime patients (8.38 days) and the difference was not significant.

Table 6: Baseline Study Characteristics

Baseline Study Characteristics		Cefepime N = 5058 (%)	Comparator N = 3976 (%)	Total N = 9034 (%)
Any pathogen recovered at baseline	No	1864(36.85)	1470(36.97)	3334(36.91)
	Yes	3194(63.15)	2506(63.03)	5700(63.09)
	Unknown	0	0	0
Pathogens isolated at baseline treatment – susceptible	No	246(4.86)	180(4.53)	426(4.72)
	Yes	2216(43.81)	1587(39.91)	3803(42.09)
	Unknown	2596(51.32)	2209(55.56)	4805(53.19)
Fungal pathogen recovered at baseline	No	4303(85.07)	3313(83.32)	7616(84.30)
	Yes	133(2.63)	127(3.19)	260(2.88)
	Unknown	622(12.30)	536(13.48)	1158(12.82)
Baseline infection mono or polymicrobial	Mono	2217(43.83)	1665(41.88)	3882(42.97)
	Poly	591(11.68)	446(11.22)	1037(11.48)
	Unknown or missing	2250(44.48)	1865(46.91)	4115(45.55)
Patient had central line at baseline	No	4374(86.48)	3421(86.04)	7795(86.29)
	Yes	432(8.54)	319(8.02)	751(8.31)
	Unknown or missing	252(4.98)	236(5.94)	488(5.40)
Renal Insufficiency or failure	No	2889(57.12)	2173(54.65)	5062(56.03)
	Yes	1317(26.04)	1134(28.52)	2451(27.13)
	Unknown	852(16.84)	669(16.83)	1521(16.84)
Hepatic insufficiency or failure	No	4311(85.23)	3380(85.01)	7691(85.13)
	Yes	6(0.12)	7(0.18)	13(0.14)
	Unknown	741(14.65)	589(14.81)	1330(14.72)
History of Diabetes	No	3537(69.93)	2696(67.81)	6233(68.99)
	Yes	585(11.57)	482(12.12)	1067(11.81)
	Unknown	936(18.51)	798(20.07)	1734(19.19)
Active cancer or malignancy (Febrile neutropenic patients only)	Solid tumor	134(2.65)	135(3.40)	269(2.98)
	Hematologic malignancy	544(10.76)	391(9.83)	935(10.35)
	Unknown/NA	4380(86.60)	3450(86.77)	7830(86.67)
Bone marrow transplant (Febrile neutropenic patients only)	No	400(7.91)	311(7.82)	711(7.87)
	Yes	179(3.54)	128(3.22)	307(3.40)
	Unknown/NA	4479(88.55)	3537(88.96)	8016(88.73)
History of COPD	No	4461(88.20)	3548(89.24)	8009(88.65)
	Yes	192(3.80)	159(4.00)	351(3.89)
	Unknown	405(8.01)	269(6.77)	674(7.46)

Table 7: Patient Treatment Discontinuation and Duration by Treatment Arm

Characteristics		Cefepime N=5058 (%)	Comparator N=3976 (%)	Total N=9034 (%)
Discontinuation	No	1278(25.2)	1014(25.5)	2292(25.37)
	Yes	3632(71.8)	2892(72.74)	6524(72.22)
	Unknown	148(2.93)	70(1.76)	218(2.41)
Duration (Days)	Mean(std)	7.46(5.28)	7.57(5.14)	7.51(5.22)
	Least-Squares Mean	8.38	8.61	
	Range(Min-Max)	1-81	1-57	1-81
	Missing	1	0	

4.2 Meta-analysis results

Table 8 shows the number of events, number of subjects available for both trial-level and patient-level analysis.

Table 8: Number of subjects available in the analysis

Analysis population	Number of studies	Cefepime # of deaths/# of pts	Control # of deaths/# of pts
Trial-level data			
Overall	88	588/9467	497/8288
Indication	88		
Febrile Neutropenia		181/2791	148/2658
Intra-abdominal		17/628	27/470
infection		186/2228	130/1821
Pneumonia		11/763	9/490
Urinary tract infection		6/335	0/165
Skin structure infection		187/2722	183/2684
Other			
Comparator Drug	88	364/5430	285/4580
Ceftazidime		58/1270	49/1140
Ceftriax		59/782	55/749
Imipene		62/965	57/976
Piperaci		37/818	41/641
Other			
Patient-level data		285/5058	226/3976
Overall	35		
Indication	35	61/776	41/626
Febrile Neutropenia		10/585	16/421
Intra-abdominal		45/609	21/306
infection		9/426	7/242
Pneumonia		6/335	0/165
Urinary tract infection		154/2327	141/2216
Skin structure infection			
Other		244/3617	185/2839
Comparator Drug	35	29/794	24/654
Ceftazidime		3/164	9/159
Ceftriax		5/59	4/57
Imipene		4/424	4/267
Piperaci			
Other		13/468	13/439
Age	35	62/2114	45/1547
0 to < 18		52/819	33/597
18 to < 55		158/1648	135/1384
55 to <65			
65 and above		118/2299	100/1772
Gender	35	167/2759	126/2204
Female			
Male		1/9	0/12
Race	35	20/724	24/563
Asian		18/783	17/594
Black		226/3212	179/2636
Hispanic		1/30	0/20
White			
Other			

Table 8: Continued

Analysis population	Number of studies	Cefepime # of deaths/# of pts	Control # of deaths/# of pts
Region	35		
US		144/3299	121/2593
Non-US		141/1759	105/1383
Any pathogen recovered at baseline	35		
Yes		200/3194	163/2506
No		85/1861	63/1470
Any pathogen isolated at baseline and susceptible to study therapy	34		
		112/2141	83/1583
Yes		31/235	8/172
No			
Baseline infection	30	127/2217	103/1665
Mono-microbial		37/586	19/446
Poly-microbial			
Fungal pathogen recovered at baseline	35		
		18/120	15/117
Yes		258/4303	199/3313
No			
Renal insufficiency or failure at baseline	35		
		115/1317	105/1134
Yes		109/2889	78/2173
No			
Active cancer or malignancy at baseline	7		
		14/134	5/135
Solid tumor		41/544	29/391
Hematologic			
Bone marrow transplant at baseline	6		
		10/179	4/128
Yes		27/400	23/311
No			

4.2.1 Trial-level data in the overall population and special subgroup of interest

Eighty-eight randomized, comparative studies were included in the trial-level analysis and a complete study list is in Appendix I. Figure 3 gives the estimated risk difference and 95% confidence intervals in the overall analysis and subgroup analysis by indication. A risk difference of greater than 0 indicates cefepime is associated with greater mortality risk compared to comparator drug. Overall, 588 out of 9467 patients in the cefepime arm died within 30 days, with an unadjusted rate of 6.21%; and 497 out of 8288 patients in the comparator arm died within 30 days, with an unadjusted rate of 6.00%. The overall risk difference was 5.38 per 1000 population (95% CI: -1.53, 12.28). The risk difference was greater than 0, but the 95% confidence interval contained the value of 0. The cefepime group had greater mortality risk compared to the comparator group, but the difference was not statistically significant.

By indication, patients with skin structure infections receiving cefepime had significantly greater mortality risk compared to those receiving comparator drug [risk difference: 17.97; 95% CI: (3.73, 32.21). However, for this indication, only two studies were available and the number of subjects was fairly small. More data is needed to confirm this observed association. The association between cefepime usage and mortality risk was not statistically significant in other indications. Patients with febrile neutropenia and pneumonia receiving cefepime had greater mortality risk compared to those receiving comparator drugs (with estimated risk difference > 0), whereas patients with intra-abdominal and urinary tract infections receiving cefepime had lower mortality risk compared to those receiving comparator drug.

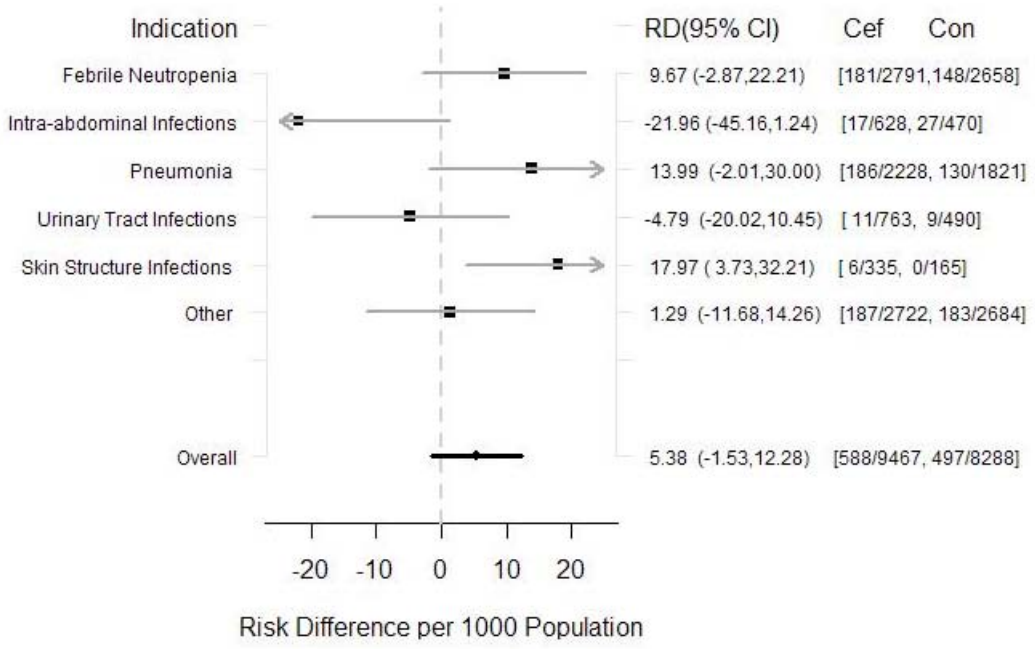


Figure 3: 30-day All-Cause Mortality Risk Difference Estimates by Indication

Figure 4 shows the estimated risk difference and 95% confidence intervals by comparator drug. For all the drug groups except for "Other", patients receiving cefepime had greater mortality risk compared to those receiving comparator drugs with estimates of risk difference from adjusted analysis greater than 0. The difference was statistically significant for cefepime versus ceftazidime comparison, but not for other comparisons. For the drug group other than 4 pre-specified drug groups, the risk difference was less than 0.

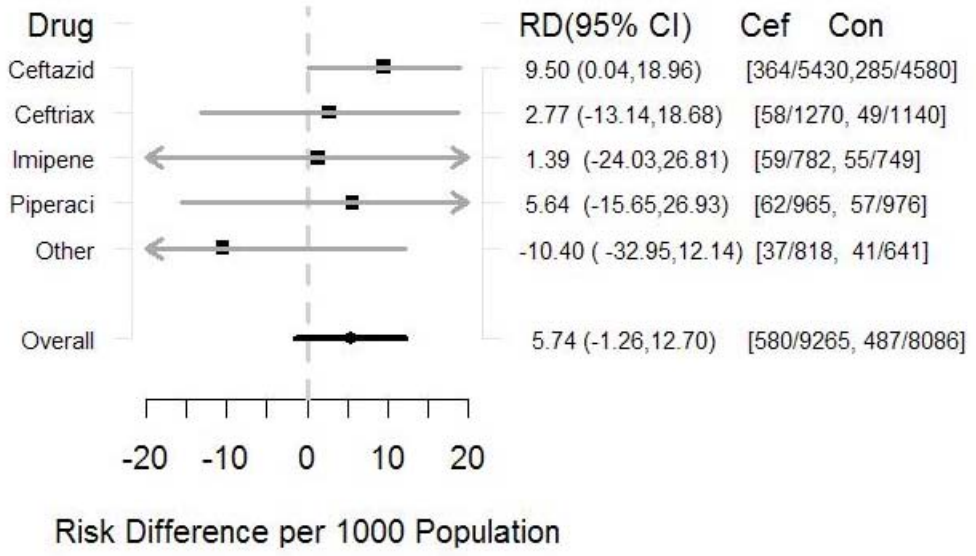


Figure 4: 30-day All-Cause Mortality Risk Difference Estimates by Comparator Drug

4.2.2 Patient-level data in the overall population and special subgroup of interest

4.2.2.1 Overall and by indication and comparator drug

35 randomized, comparative studies were included in the patient-level analysis and a complete study list can be found in Appendix I. The dosing regimens vary from 0.5 – 2 gram every 8-12 hours. So the first step in the analysis of the pooled dataset was to determine whether there was any evidence of dose-response for cefepime. The effect was not significant (p = 0.61). Because there was no notable evidence of a dose response, dose effect was not taken into account in the analyses. Figure 5 gives the estimated risk difference and 95% confidence intervals in the overall analysis and subgroup analysis by indication. The analysis yields similar conclusions as the trial-level analysis. Overall, 285 out of 5058 patients in the cefepime arm died within 30 days, with an unadjusted rate of 5.63%; and 226 out of 3976 patients in the comparator arm died within 30 days, with an unadjusted rate of 5.68%. The overall risk difference was 4.83 per 1000 population (95% CI: -4.72, 14.38). The risk difference was greater than 0, but the 95% confidence interval contained the value of 0. The cefepime group had greater mortality risk compared to the comparator group, but the difference was not statistically significant.

Subgroup analyses were conducted in patients with complete information for the specific factors.
As was found in the trial-level analysis, cefepime treatment in patients with skin structure infections was associated with significantly greater mortality risk compared to those receiving comparator drug [risk difference: 17.97; 95% CI: (3.73, 32.21). The association between cefepime usage and mortality risk was not statistically significant in other indications. Patients with febrile neutropenia and pneumonia receiving cefepime had greater mortality risk compared to those receiving comparator drug (with estimated risk difference > 0), whereas patients with intra-abdominal and urinary tract infections receiving cefepime had lower mortality risk compared to those receiving comparator drug. However, these differences were not found to be statistically significant.

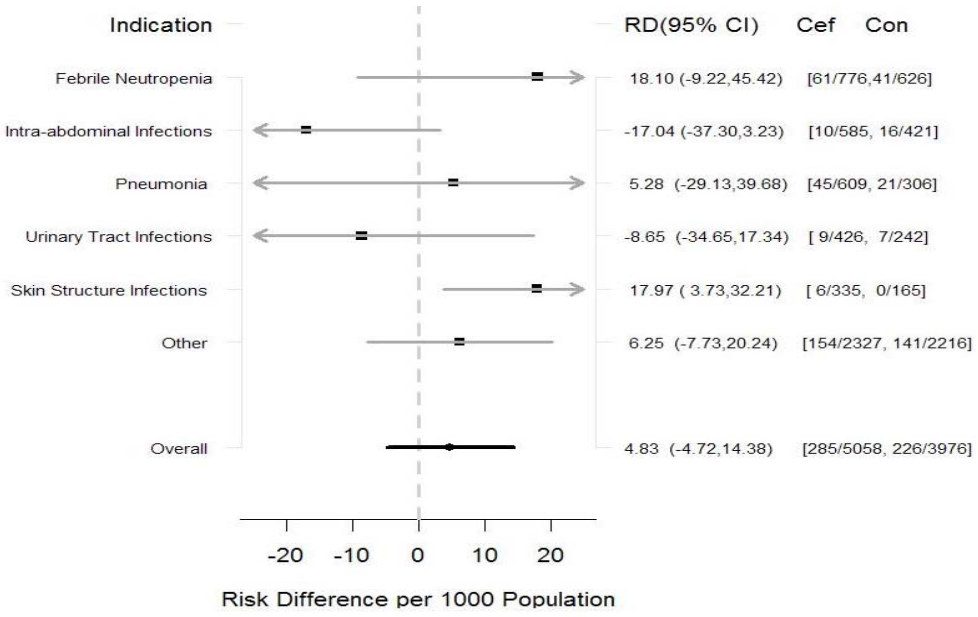


Figure 5: 30-day All-Cause Mortality Risk Difference Estimates by Indication

Figure 6 shows the estimated risk difference and 95% confidence intervals by comparator drug. Patients treated with cefepime had greater mortality risk compared to those taking ceftazidime and piperacillin-tazobactam, whereas the risks were lower for patients taking other comparator drugs. The differences were not significant in all drug groups.

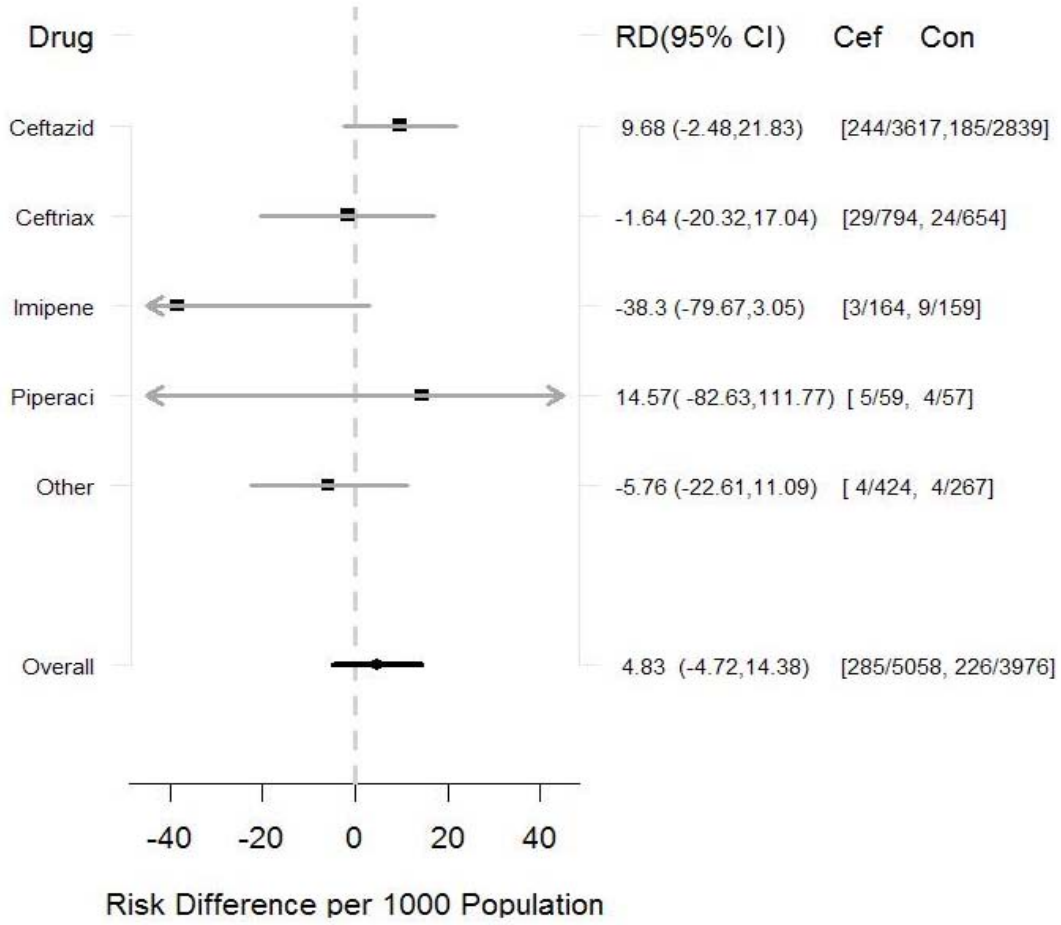


Figure 6: 30-day All-Cause Mortality Risk Difference Estimates by Comparator Drug

4.2.2.2 Age

Figure 7 shows the estimated risk difference and 95% confidence intervals by age group. Cefepime use was associated with greater mortality risk compared to comparator drug for patients aged ≥ 18 years old, although these associations was not found to be statistically significant. Overall, there was no clear pattern across age groups.

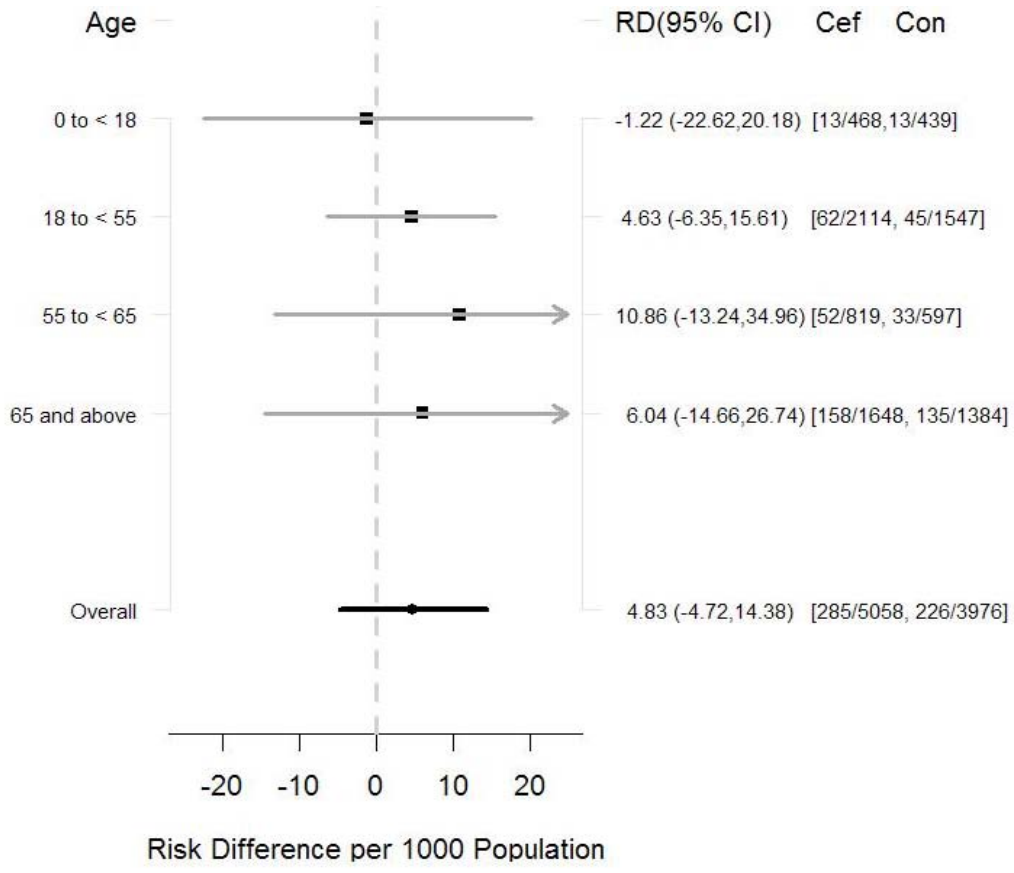


Figure 7: 30-day All-Cause Mortality Risk Difference Estimates by Age

4.2.2.3 Gender

Figure 8 displays the estimated risk difference and 95% confidence intervals by gender. Cefepime treatment was associated with greater mortality risk compared to comparator drug for both male and female groups, but the differences were not found to be statistically significant.

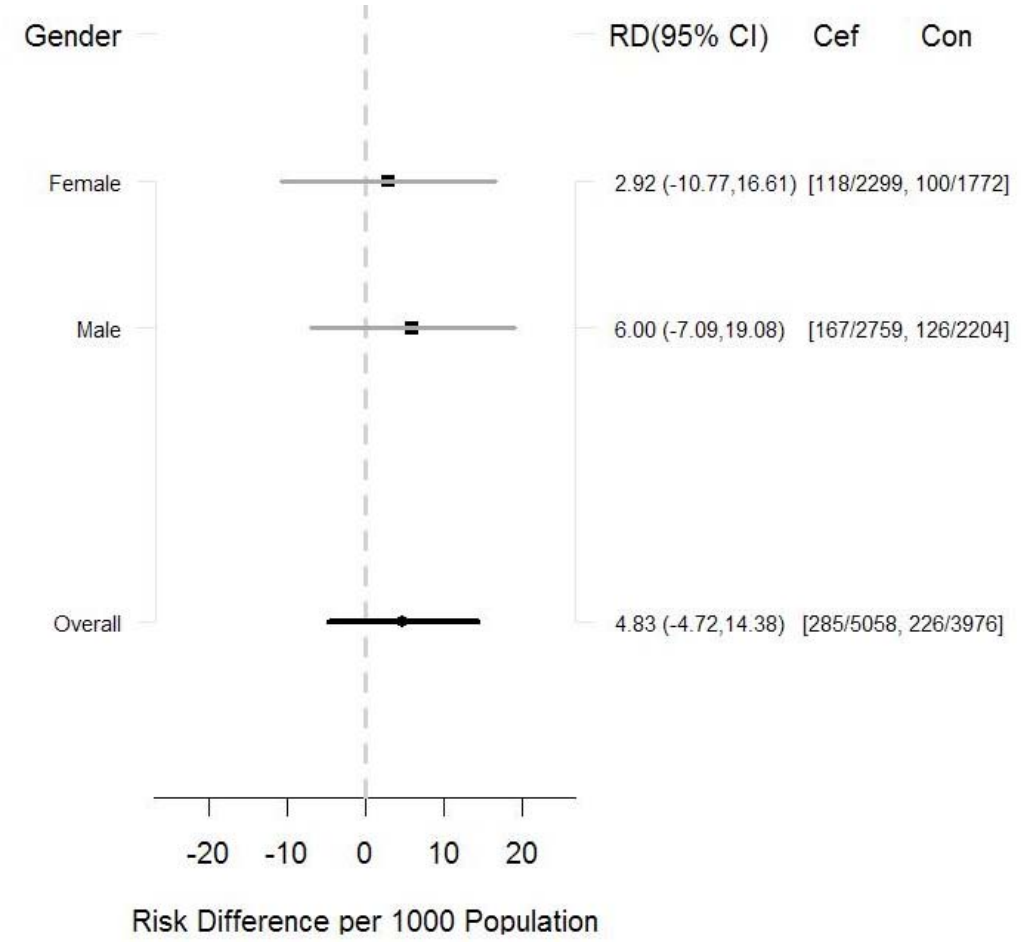


Figure 8: 30-day All-Cause Mortality Risk Difference Estimates by Gender

4.2.2.4 Race

Figure 9 gives the estimated risk difference and 95% confidence intervals by race. 65% of the study population was Caucasian. Cefepime treatment was associated with greater mortality risk compared to comparator drug treatment for Caucasians, but not for other race groups, except for Asians. However, Asians had very few patients resulting in wide confidence interval. Cefepime treatment was associated with lower mortality risk compared to comparator drug treatment for Blacks and Hispanics. The differences were not significant for all race groups.

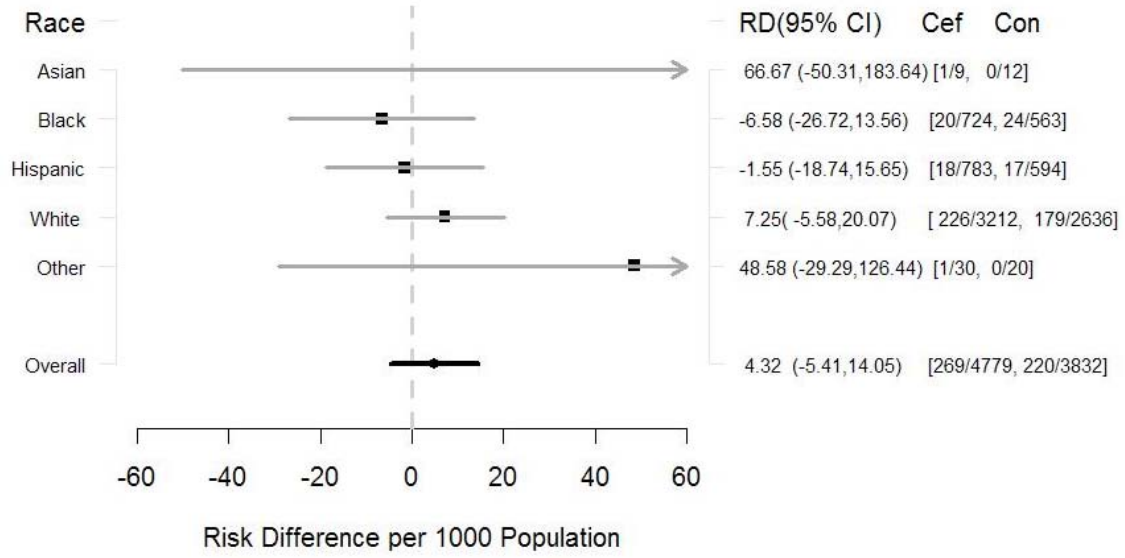


Figure 9: 30-day All-Cause Mortality Risk Difference Estimates by Race

4.2.2.5 Region

Figure 10 shows the estimated risk difference and 95% confidence intervals by location. 65% of the study population was from the US population. For both US and non-US populations, the estimated risk differences were greater than 0. However, the estimate for the non-US population was notably larger. The differences were not significant for either group.

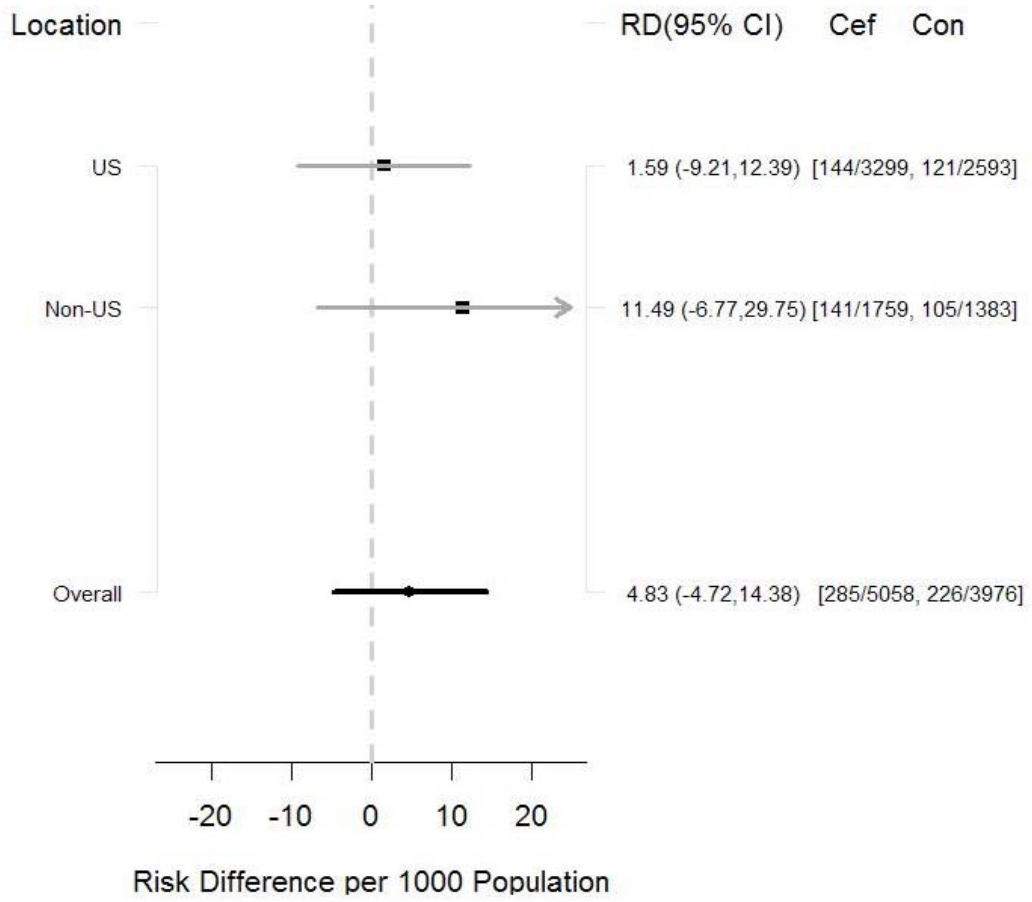


Figure 10: 30-day All-Cause Mortality Risk Difference Estimates by Location

4.2.2.6 Any pathogen recovered at baseline

Figure 11 displays the estimated risk difference and 95% confidence intervals by pathogen status. For both groups, the estimated risk differences were greater than 0 and the values were similar. The differences were not significant for either group.

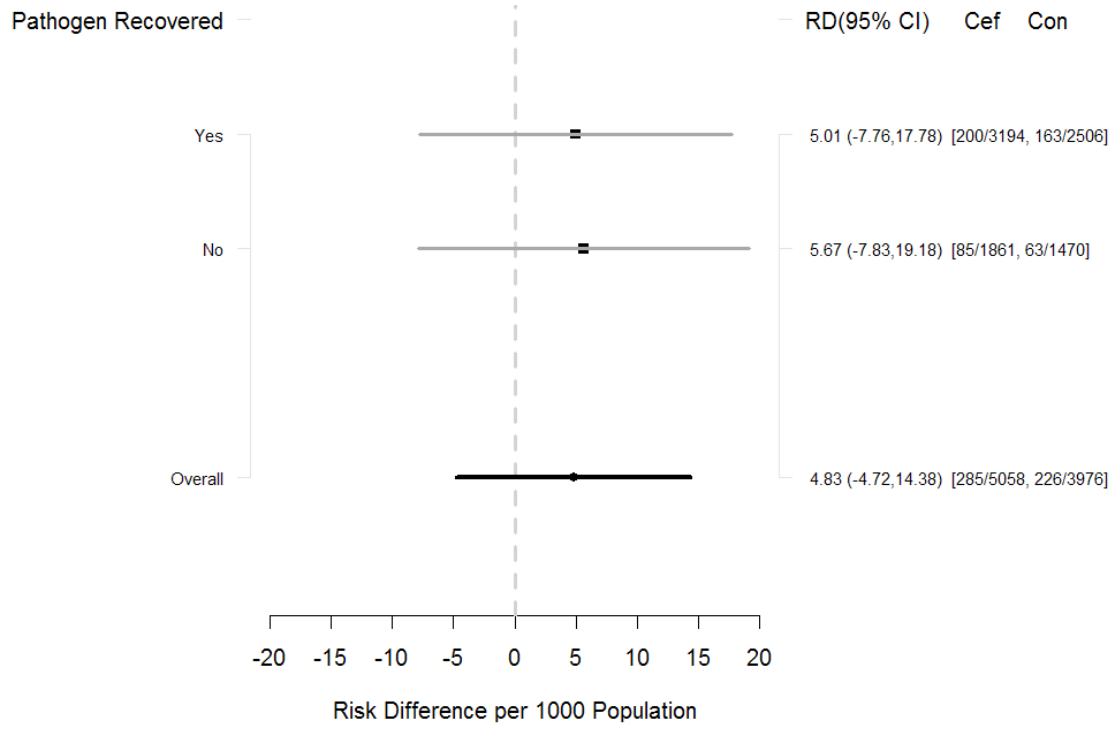


Figure 11: 30-day All-Cause Mortality Risk Difference Estimates by Pathogen Status

4.2.2.7 Any pathogen isolated at baseline and susceptible to study therapy

Figure 12 gives the estimated risk difference and 95% confidence intervals by pathogen susceptibility to study therapy. Cefepime-treated patients with pathogens isolated at baseline resistant to study therapy had a risk difference greater than 0 (67.47 per 1000 population) compared to comparator-treated patients with pathogens isolated at baseline with resistance to comparator drugs. This difference was found to be statistically significant (95% CI: 16.30, 118.61). Due to the small number of patients in this group, the confidence interval was very wide. Exploratory analyses were conducted for patients with pathogen resistance at baseline to investigate potential risk factors which may contribute to the causes of excess death in this sub-population. From all factors we examined, there was no clear pattern that any particular factor could provide an explanation for the excess death observed in the cefepime group. The results are shown in Appendix II.

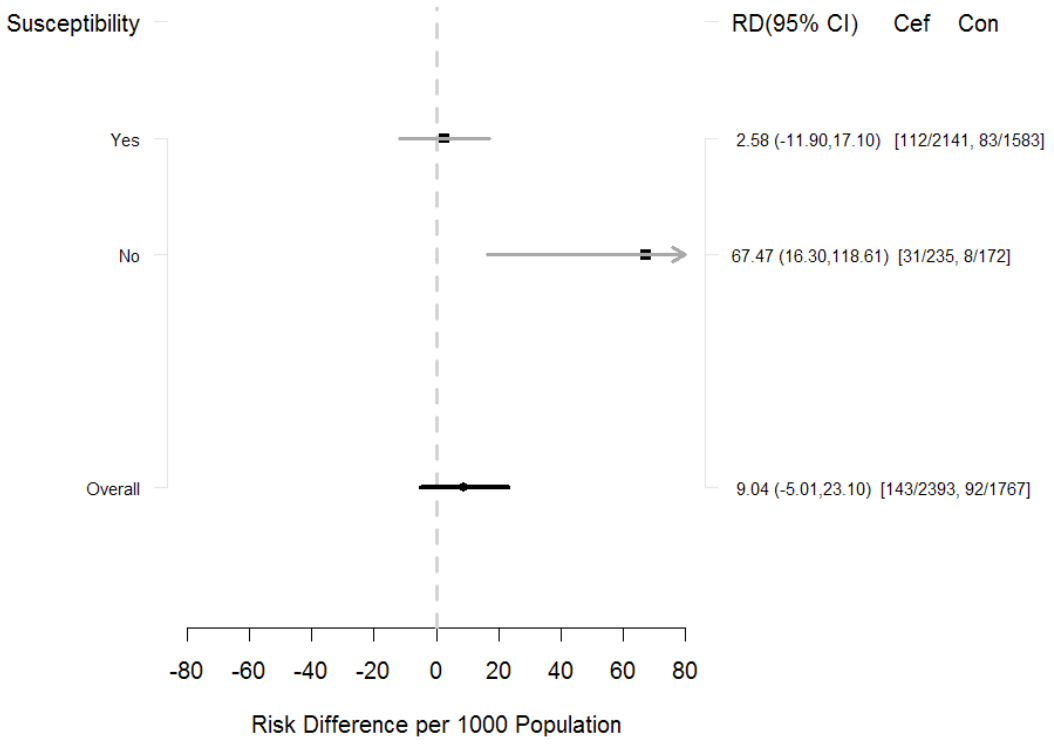
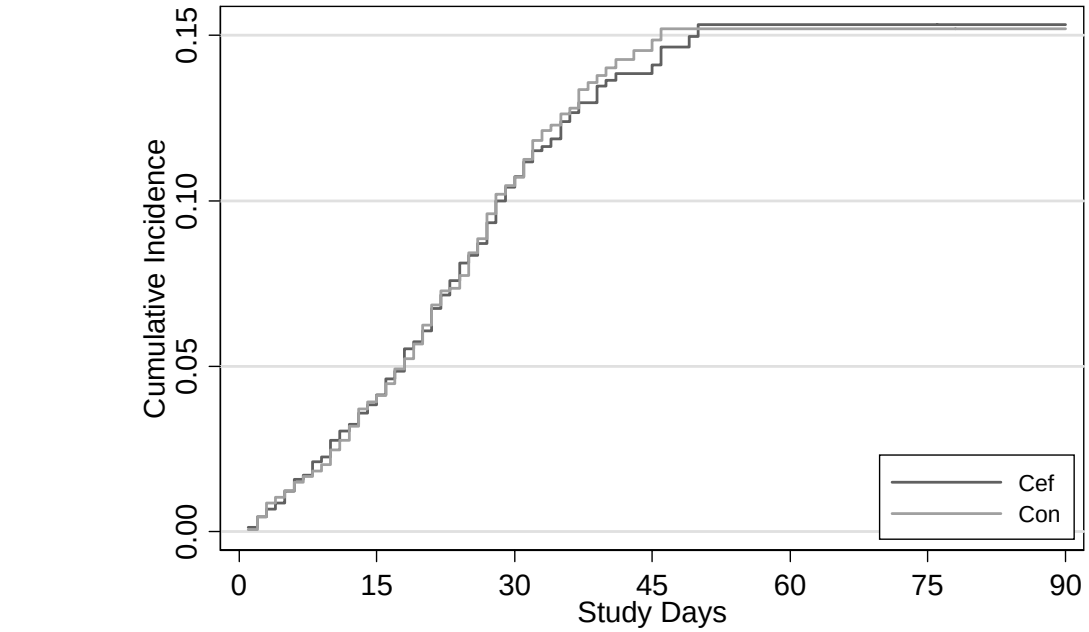


Figure 12: 30-day All-Cause Mortality Risk Difference Estimates by Pathogen Susceptibility to Study Therapy

4.2.2.8 Hazard pattern

Figure 13 shows the Kaplan-Meier cumulative incidence curves for the 30-day post-therapy all-cause mortality in the overall population. The x-axis is the study days and y-axis is the cumulative incidence rate (%). All events happened prior to study day 60. From a visual inspection of the curves, it appears that cefepime group had slightly lower incidence rates compared to the comparator group after 30-days in the study but the difference was very small and not significant.



Number at risk

Cef	5058	2651	948	390	163	93	71
Con	3976	2109	768	314	122	73	54

Figure 13: Kaplan-Meier Cumulative Incidence Curves in the Overall Population

4.3 Post-hoc analysis in the patient-level data

Subgroup analyses were conducted for five additional baseline factors, including baseline infection, fungal pathogen recovered at baseline, renal insufficiency or failure at baseline, active cancer or malignancy (febrile neutropenic patients only), bone marrow transplant (febrile neutropenic patients only).

4.3.1 Baseline infection

Figure 14 gives the estimated risk difference and 95% confidence intervals by baseline infection. For both mono- and poly-microbial groups, the estimated risk differences were greater than 0. For the poly-microbial group, the estimate of risk difference was notably larger and the confidence interval was very wide. The differences were not significant for either group.

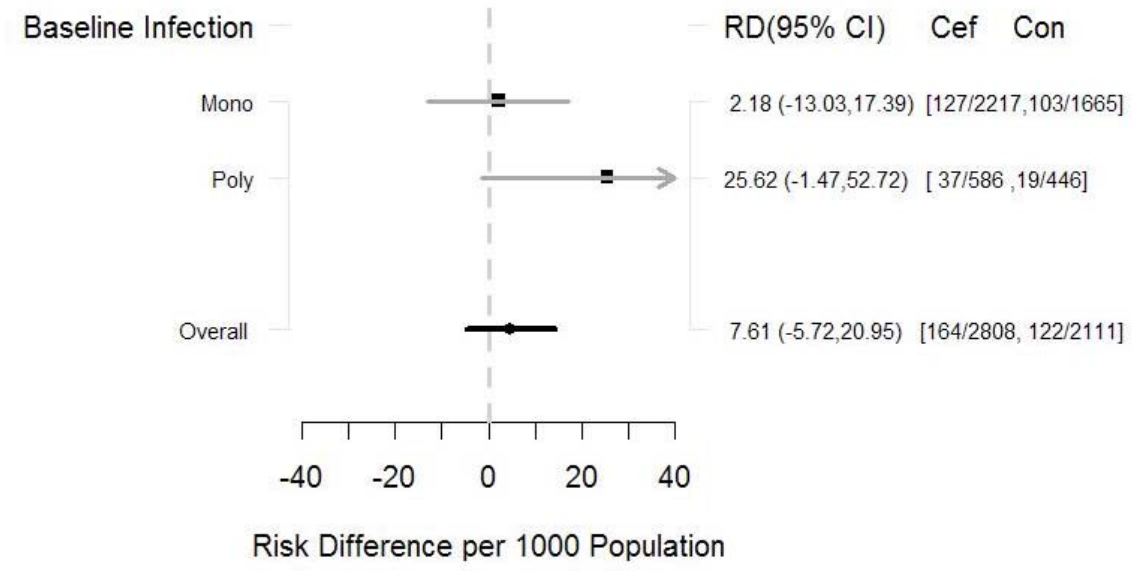


Figure 14: 30-day All-Cause Mortality Risk Difference Estimates by Baseline Infection

4.3.2 Fungal pathogen recovered at baseline

Figure 15 shows the estimated risk difference and 95% confidence intervals by fungal pathogen recovered at baseline. For both groups, the estimated risk differences were greater than 0. For subjects with fungal pathogen recovered at baseline, the estimate was notably larger, but the confidence interval was very wide due to small number of subjects in the group. The differences were not significant for either group.

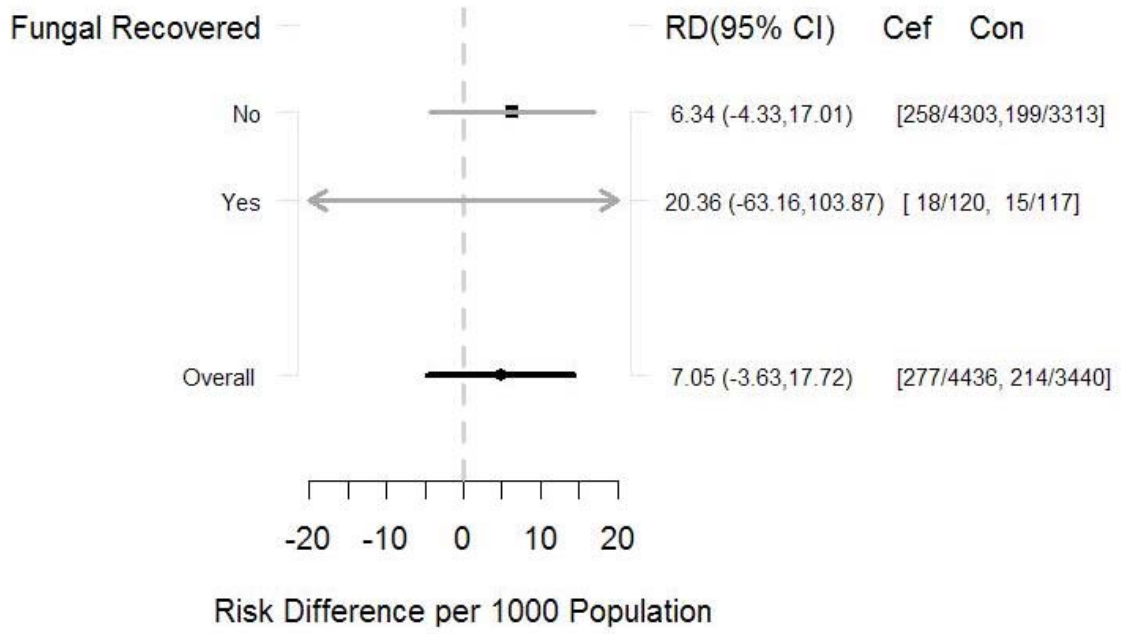


Figure 15: 30-day All-Cause Mortality Risk Difference Estimates by Fungal Pathogen Recovery

4.3.3 Renal insufficiency or failure at baseline

Figure 16 displays the estimated risk difference and 95% confidence intervals by renal status. For both groups, the estimated risk differences were greater than 0 and the differences were not significant for either group.

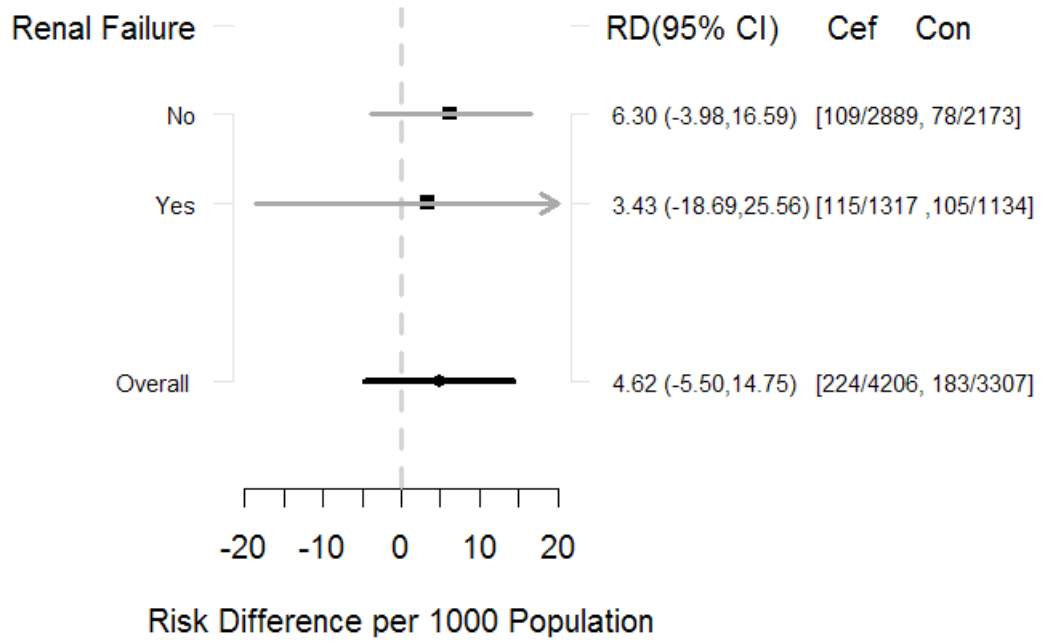


Figure 16: 30-day All-Cause Mortality Risk Difference Estimates by Renal Status

4.3.4 Active cancer or malignancy at baseline

Figure 17 shows the estimated risk difference and 95% confidence intervals by cancer status. The information on cancer status was collected for febrile neutropenic patients only. Patients with solid tumors had significantly greater mortality risk in the cefepime group compared to comparator group (risk difference: 69.74 per 1000 population; 95% CI: (8.13, 131.35)). The confidence interval was very wide due to the small number of subjects. The risk difference was also greater than 0 in the hematologic cancer group, but the difference was not significant.

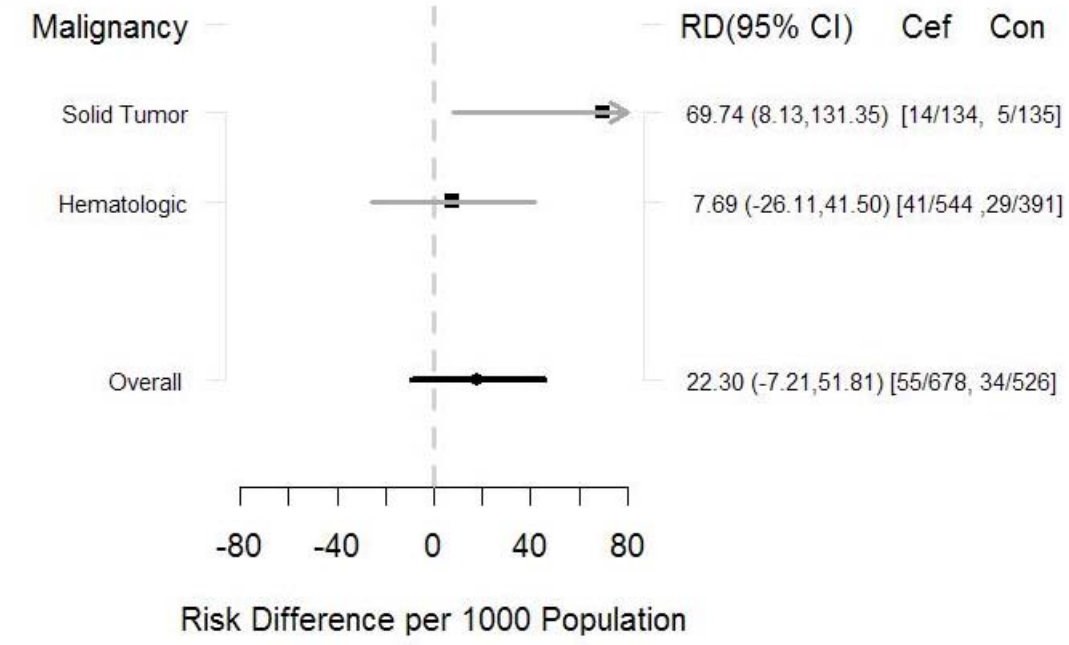


Figure 17: 30-day All-Cause Mortality Risk Difference Estimates by Cancer Status

4.3.5 Bone marrow transplant at baseline

Figure 18 shows the estimated risk difference and 95% confidence intervals by bone marrow transplant status. The information on bone marrow transplant status was collected for febrile neutropenic patients only. Patients with bone marrow transplant had risk difference greater than 0, whereas patients without bone marrow transplant had risk difference smaller than 0. The differences were not significant in either group.

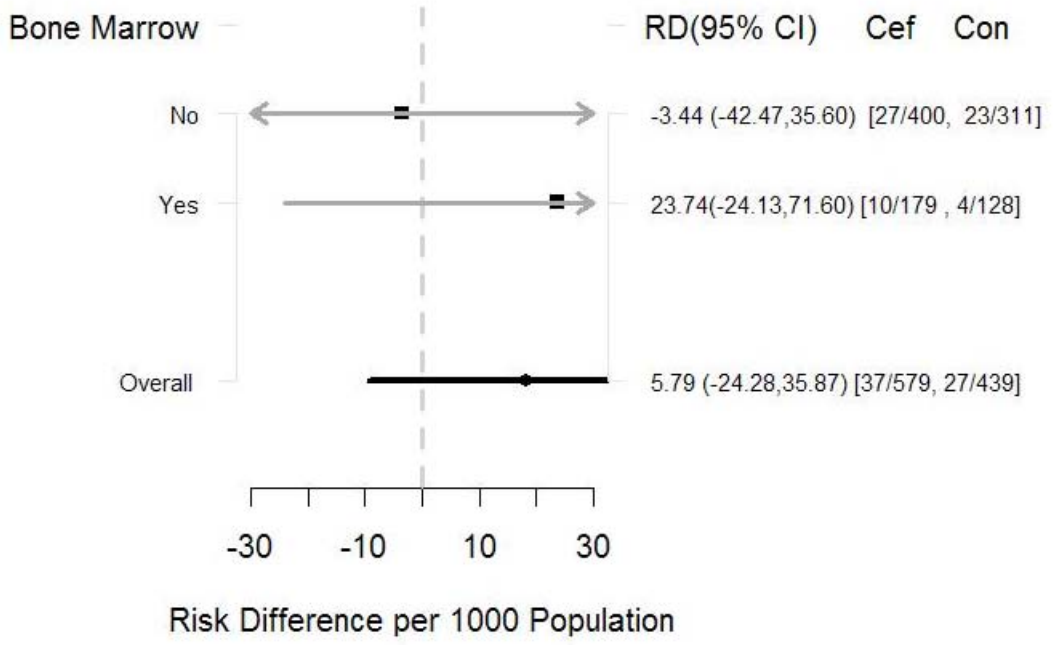


Figure 18: 30-day All-Cause Mortality Risk Difference Estimates by Bone Marrow Transplant Status

4.4 Sensitivity analysis

4.4.1 Inclusion of trials with less than 10 subjects per am

Statistical analyses were repeated in the study population which includes studies with less than 10 subjects per arm to examine the impact of these small trials. The forest plots (Figures 20 & 21) are shown in Appendix II. The results were very similar with those from the primary analysis. The inclusion of additional small studies did not have substantial impact on the analysis results.

4.4.2 Method Sensitivity

Several alternative statistical methods were applied to test the robustness of the primary statistical method. Exact and Mantel-Haenszel methods of odds ratio were employed to assess the sensitivity of results based on risk difference analysis. Table 10 in Appendix II shows the results in the overall and subgroup analyses. In the overall analysis, both methods gave the estimate of odds ratio as 1.10 with 95% confidence interval including 1 which suggests that cefepime was associated with slightly greater mortality risk compared to the comparator drugs, but the difference was not significant. This result is consistent with that of the primary analysis. Also, in

the subgroup analysis, the results using odds ratio method were consistent with the results using risk difference method. Our primary statistical method, Mantel-Haenszel risk difference, gave robust results in both overall and subgroup analyses.

Stratified risk ratio and 95% confidence interval using person-time units and a Cox proportional hazards model stratified by trial were also conducted to examine the consequences of the possibility of non-constant hazards and/or differential follow-up between the treatment arms. Both analyses yield very similar results [exact RR (95% CI): 0.94 (0.78, 1.12); hazards ratio (95% CI): 0.96(0.80, 1.15)] which suggest that the mortality risks were similar in cefepime and comparator groups and the difference was not significant. The difference in the direction of point estimate between risk difference and risk ratio methods could possibly explained by the differential hazard pattern over time as shown by figure 11. However, the adjusted estimates all lay close to cut-off point (0 for risk difference measure and 1 for risk ratio measure), and the 95% confidence intervals all included the cut-off point.

4.4.3 Microbiological ITT population

All analyses, using different statistical methods in both overall and subgroup analyses, were repeated in the microbiological ITT population and the results are shown in Appendix II. Figure 19 gives the estimated risk difference and 95% confidence intervals in the overall population and by indication. Overall, 199 out of 3205 patients in the cefepime arm died within 30 days, with an unadjusted rate of 6.21%; and 161 out of 2527 patients in the comparator arm died within 30 days, with an unadjusted rate of 6.37%. The overall risk difference was 5.71 per 1000 population (95% CI: -6.95, 18.37). The risk difference was greater than 0, but the 95% confidence interval contained the value of 0. This result is consistent with the analysis results of the safety ITT population. Cefepime group had greater mortality risk compared to the comparator group, but the difference was not statistically significant.

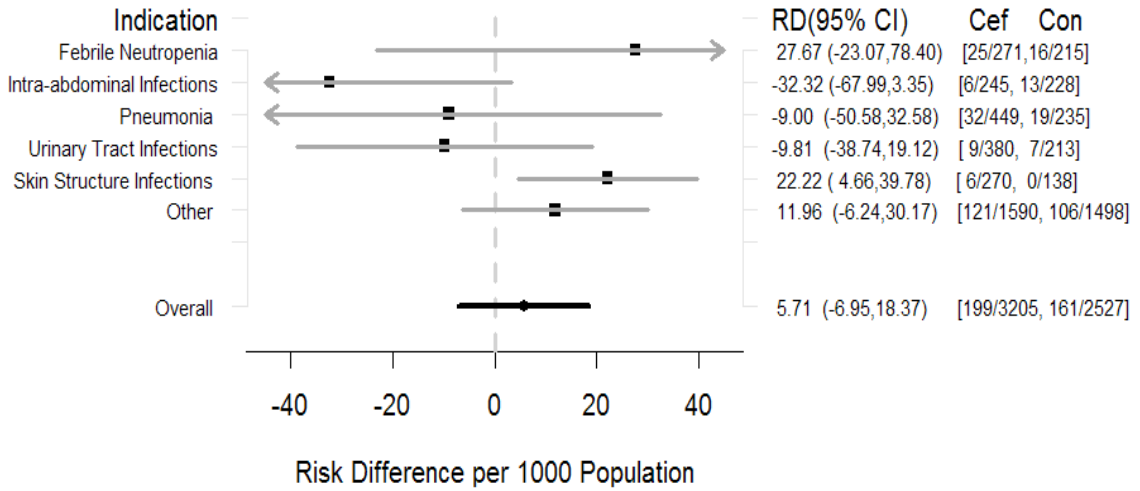


Figure 19: 30-day All-Cause Mortality Risk Difference Estimates by Indication in the Microbiological ITT population

Table 11 in Appendix II gives the analysis results using exact OR, Mantel-Haenszel OR and RD methods for other subgroups. The main results were consistent with the findings in the safety ITT population. Cefepime treatment was associated with significantly greater mortality risk compared to comparator drugs for the indication of skin structure infections and for patients with pathogens

isolated at baseline resistant to study therapy. However, the 95% confidence intervals were very wide due to the small number of subjects in the group.

5 SUMMARY AND CONCLUSIONS

5.1 Summary

This review examines the association of cefepime with mortality risk through a meta-analysis study. The meta-analysis is based on both trial-level and patient-level data from clinical trials available to the sponsor. A total of 88 randomized, controlled studies (cefepime: 9467; comparator: 8288) are included in the trial-level analysis and 35 randomized, controlled studies (cefepime: 5058, comparator: 3976) are available in the patient-level analysis. The primary objectives are to examine if 1) cefepime is associated with an increased risk of mortality relative to comparator drugs in randomized controlled trials, 2) the risk of mortality varies by (a) indication, (b) comparator drug or drug groups, (c) baseline risk factor subgroups, and d) demographic subgroups. The primary endpoint is 30-day post-therapy all-cause mortality and the primary statistical method is the Mantel-Haenszel Risk difference method stratified by trial.

In the overall analysis, both trial-level and patient-level gave similar conclusions that cefepime was associated with greater mortality risk compared to comparator, but the difference was not significant. The risk difference estimate for the trial-level analysis was 5.38 per 1000 population (95% CI: (-1.53, 12.28)) and for the patient-level analysis was 4.83 per 1000 population (95% CI: (-4.72, 14.38)). Sensitivities analyses in different study populations and using alternative statistical methods gave similar findings.

In the subgroup analysis, there was no significant effect for most factors we examined, except for the indication of skin structure infections [RD estimate: 17.97 per 1000 population, 95% CI: (3.73, 32.21)], patients with pathogens isolated at baseline resistant to study therapy [RD estimate: 67.47 per 1000 population, 95% CI: (16.30, 118.61)] and febrile neutropenia patients with solid tumor at baseline[RD estimate: 69.74 per 1000 population, 95% CI: (8.13, 131.35)]. The numbers of subjects available in these subgroups were very small, thus resulting in wide confidence intervals. Therefore, significant findings from these subgroups need to be re-examined when more data is available. In summary, patients with febrile neutropenia, pneumonia and skin structure infections who received cefepime had greater mortality risk compared to those receiving comparator drugs. Patients treated with cefepime had greater mortality risk compared to those treated with ceftazidime and piperacillin-tazobactam. The risk difference estimates for patients aged $\geq$ 18 years old were greater than 0. Both male and female groups had positive risk differences. Caucasians comprised 65% of the study population and were the only subgroup with risk difference greater than 0, besides Asians. However, Asians comprised only 0.25% of study population so that the confidence interval was very wide. Both US and non-US populations had positive risk differences, but the estimate in the non-US population was notably larger.

From an examination of the Kaplan-Meier cumulative incidence curves, the incidence rates were very similar in both cefepime and comparator groups throughout the study period.

Several sensitivity analyses were performed to examine the robustness of the primary results to the inclusion of small trials, to microbiological ITT population, and to statistical methods. The inclusion of small trials did not substantially affect the overall estimate. All analyses in the

microbiological ITT population showed findings consistent with the primary results from the safety ITT population. Various statistical methods also gave similar findings as did our primary analysis method.

There are several limitations in this meta-analysis. First, for most analyses, the unit of analysis was by subject. However, in some febrile neutropenic studies, the unit of analysis was by episode of neutropenia when the information on the number of subjects was not available. Second, the numbers of subjects available in subgroups with significant findings were very small, thus resulting in wide confidence intervals which made interpretation and further analyses difficult. Therefore, significant findings from these subgroups need to be re-examined when more data is available. Third, some information which could possibly affect the study results was not available; thus it was not considered in the analysis, for example, information on concomitant antibiotics and the ascertainment of primary endpoint. Last, some studies, mainly from the conference abstract or publications, included in the trial-level analyses had missing information on the study indication, therefore, these studies were categorized to the "other" group in the by indication subgroup analysis.

5.2 Conclusions

This meta-analysis shows that cefepime was associated with greater mortality risk compared to the comparator drug, but the difference was not significant. Yahav's analysis was based on 41 studies which were a subset of our trial-level data. The safety concern raised by Yahav's paper was not confirmed in our comprehensive data analysis. Cefepime was associated with significantly greater mortality risk compared to comparator drug in the indication of skin structure infections, patient with pathogens isolated at baseline resistant to study therapy and febrile neutropenic patients with solid tumor at baseline. Due to small number of subjects in these subgroups, additional clinical studies may be required to evaluate the risk of cefepime in these subgroups.

REFERENCES

1. Yahav D, Paul M, Fraser A, Sarid N & Leibovici L. Efficacy and safety of cefepime: a systematic review and meta-analysis. Lancet Infect Dis 2007; 7:338-48.
2. Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. Biometrics 1985; 41: 55-68.
3. Agresti A. A Survey of Exact Inference for Contingency Tables. *Statistical Science* 1992; 7:131- 177.

Appendix I Trials Included in the Analysis

Study No. or Yahav Ref No.	Indication	Cefepime # of death / # of pts	Comparator # of death / # of pts	Comparator drug name	Patient-level data available (Y/N)	Study included in Yahav paper (Y/N)
BMS Clinical Trials						
AI411132	Bone & Joint	0/23	0/10	Antibiotic	Y	Y
AI411079	Dose tolerance	0/20	0/20	Ceftriaxone	N	N
AI411118	FN	5/59	4/57	Piperacillin/ gentamycin	Y	N
AI411137	FN	0/35	1/36	Mezlocillin/ gentamycin	Y	N
AI411186	FN	13/242	4/111	Ceftazidime/ amikacin	Y	Y
AI411189	FN	8/139	10/142	Ceftazidime	Y	Y
AI411198	FN	5/53	3/58	Ceftazidime/ vancomycin	Y	Y
AI411204	FN	22/143	10/133	Ceftazidime	Y	Y
AI411131	FN	9/94	6/100	Ceftazidime	Y	Y
AI411178	Intra-abdominal	1/13	0/8	Gentamycin/ clindamycin	Y	N
AI411179	Intra-abdominal	3/34	0/17	Gentamycin/ mezlocillin	Y	N
AI411206	Intra-abdominal	4/32	4/31	Ceftoxime/ metronidazole	Y	N
AI411221	Intra-abdominal	3/164	11/159	Imipenem/cil-astatin	Y	N
AI411119	Intra-abdominal	1/114	1/93	Gentamycin/ clindamycin	Y	N
AI411120	Intra-abdominal	0/241	2/121	Gentamycin/ mezlocillin	Y	N
AI411070	LRTI	26/387	16/194	Ceftazidime	Y	Y
AI411106	LRTI	13/53	5/27	Cefotaxime	Y	Y
AI411113	LRTI	4/114	0/57	Ceftazidime	Y	N
AI411097	MSI	30/627	34/622	Ceftazidime	Y	Y
AI411111	MSI	32/173	26/175	Ceftazidime	Y	Y
AI411123	Pediatric	0/20	0/8	Cefuroxime	Y	N
AI411126	Pediatric	3/69	6/66	Cefotaxime	Y	Y
AI411157	Pediatric	0/22	0/12	Cefotaxime	Y	N
AI411194	Pediatric	0/3	0/1	Ceftriaxone	Y	N
AI411212	Pediatric	7/105	5/105	Ceftriaxone	Y	Y
AI411220	Pediatric	0/31	0/26	Cefotaxime	Y	Y
AI411224	Pediatric	0/1	0/2	Ceftriaxone	Y	N
AI411056	Single dose	0/37	0/37	Ceftazidime	N	N
AI411127	Single dose	0/6	0/6	Ceftazidime/ cefoperazone	N	N
AI411154	PK	0/16	0/16	Amikacin	N	N
AI411075	SSTI	1/104	0/50	Ceftazidime	Y	N
AI411081	SSTI	5/231	0/115	Ceftazidime	Y	Y
AI411071	UTI	0/32	1/16	Ceftazidime	Y	N
AI411083	UTI	8/305	6/161	Ceftazidime	Y	Y
AI411108	UTI	1/39	0/41	Ceftazidime	Y	Y
AI411121	UTI	0/159	0/72	Cefotaxime	Y	Y

(Continued)

Study No. or Yahav Ref No.	Indication	Cefepime # of death / # of pts	Comparator # of death / # of pts	Comparator drug name	Patient-level data available (Y/N)	Study included in Yahav paper (Y/N)
BMS Unpublished Studies						
AI411242	FN	8/76	11/68	Piperacillin/ tazobactam/ amikacin	N	N
CPM2295002	FN	10/202	4/198	Imipenem/ cilastatin	N	Y
CPM2393002	FN	2/58	1/52	Ceftazidime/ Amikacin	N	Y
CPM6195013	FN	3/95	4/85	Imipenem	N	Y
CPM6796002	FN	13/98	13/97	Ceftazidime/ Amakacin	N	N
CPM0896003	Intra-abdominal	0/14	2/18	Ceftriazone	N	N
CPM4497002	Intra-abdominal	6/29	7/31	Cefotaxime/m etronidazole	N	N
AI411168	LRTI	2/64	1/34	Ceftazidime	N	N
AI411197	LRTI	1/4	2/6	Ceftazidime	N	N
AI411222	LRTI	1/16	3/19	Ceftazidime/ Amikacin	N	N
CPM6796007	LRTI	2/22	1/23	Sulbactam/cef operazone	N	N
AI411152	LRTI/pneumonia	2/57	0/29	Ceftazidime	Y	Y
AI411174	LRTI/pneumonia	2/94	1/89	Ceftazidime	N	Y
AI411196	LRTI/pneumonia	10/59	13/61	Ceftazidime	N	N
AI411200	LRTI/pneumonia	3/59	1/56	Ceftriaxone	N	Y
AI411201	LRTI/pneumonia	5/56	2/55	Cefotaxime	N	N
AI411205	LRTI/pneumonia	8/85	12/82	Imipenem/ cilastatin	N	N
AI411227	LRTI/pneumonia	7/76	7/75	Ceftriaxone	N	Y
AI411237	LRTI/pneumonia	28/108	19/101	Imipenem/ cilastatin	N	Y
CPM2293004	LRTI/pneumonia	29/141	21/134	Ceftazidime/ Amikacin	N	N
CPM3694007	LRTI/pneumonia	0/77	0/71	Ceftazidime	N	Y
CPM4495001	LRTI/pneumonia	2/15	2/15	Ceftazidime	N	N
CPM5995012	LRTI/pneumonia	1/84	2/76	Cefotaxime	N	Y
AI411160	MSI	35/421	22/419	Ceftazidime	Y	Y
AI411184	MSI	3/35	2/36	Ceftazidime	Y	N
AI411219	MSI	41/181	44/185	Ceftazidime/ Amikacin	Y	N
AI411228	MSI	12/82	25/76	Targeted therapy	N	N
AI411230	MSI	3/307	4/308	Ceftriaxone	Y	N
AI411245	MSI	17/159	10/158	Broad spectrum therapy	N	N
AI411213	Pediatric	0/181	1/181	Ceftazidime	Y	N

(Continued)

Study No. or Yahav Ref No.	Indication	Cefepime # of death # of pts	Comparator # of death # of pts	Comparator drug name	Patient-level data available (Y/N)	Study included in Yahav paper (Y/N)
BMS Unpublished Studies						
AI411172	RTI	0/83	0/87	Ceftazidime	N	Y
AI411169	UTI	1/119	0/123	Ceftazidime	N	N
AI411235	Pediatric	0/149	0/150	Ceftazidime	N	Y
AI411247	RTI	2/218	1/225	Ceftazidime	N	N
AI411149	UTI	0/50	0/24	Ceftazidime	Y	N
Non-BMS studies						
44	LRTI	0/30	0/30	Ceftazidime	N	N
45	FN	0/32	0/31	Ceftazidime	N	Y
26	FN	3/47	2/46	Ceftazidime	N	Y
61	FN	19/432	27/435	Piperacillin/tazobactam	N	Y
54	Bacterial infection	1/25	2/25	Ceftazidime	N	Y
20	FN	2/49	2/51	Piperacillin/tazobactam	N	Y
66	FN	2/42	1/41	Carbapenem	N	Y
32	FN	13/98	13/97	Ceftazidime/ Amikacin	N	Y
31	Pneumonia	3/40	0/22	Ceftazidime	N	Y
42	RTI	0/50	0/50	Sulbactam/cefoperazone	N	N
68	Pneumonia	5/54	2/55	Cefotaxime	N	Y
29	FN	8/202	10/202	Meropenem/pip/tazo+amino-glycoside	N	Y
30	FN	1/100	2/107	Ceftriaxone/gentamicin	N	Y
24	Bacterial infection	0/20	0/16	Ceftazidime	N	N
37	FN	13/86	5/100	Piperacillin/tazobactam+amikacin	N	Y
56	FN	7/127	5/124	Imipenem	N	Y
67	FN	0/19	2/22	Ceftazidime	N	Y
22	FN	15/263	8/265	Piperacillin/tazobactam	N	Y
48	Pneumonia	2/41	0/20	Ceftazidime	N	N
18	Pneumonia	29/141	21/134	Ceftazidime/ Amikacin	N	Y
41	Severe infections	2/26	0/26	Ceftazidime	N	Y
63	Bacterial infections	1/13	2/15	Ceftazidime	N	Y
34	UTI	1/59	2/53	Ceftazidime	N	Y

Abbreviations: FN = Febrile Neutropenia, UTI = urinary tract infection; RTI = respiratory tract infection; LRTI = lower respiratory tract infection; MSI = multiple serious infections; SSTI = skin and skin structure infection; PK = pharmacokinetic

Appendix II

Table 9: Demographic and pathogen infections for subjects with resistant pathogens at baseline

	Alive			Death		
	Total # of pts(%)	Cef # of pts(%)	Con # of pts(%)	Total # of pts(%)	Cef # of pts(%)	Con # of pts(%)
Indication						
Febrile neutropenia	86(22.5)	46(21.5)	40(23.7)	7(17.5)	4 (12.9)	3(33.3)
Intra-abdominal	81(21.2)	37(17.3)	44(26.0)	0	0	0
LRTI	7(1.8)	5(2.3)	2(1.2)	2(5.0)	2 (6.5)	0
UTI	15(3.9)	8(3.7)	7(4.1)	2(5.0)	2 (6.5)	0
SSTI	21(5.5)	12(5.6)	9(5.3)	1(2.5)	1 (3.2)	0
Mixed infect	90(23.5)	53(24.8)	37(21.9)	24(60.0)	19(61.3)	5(55.6)
Other	83(21.7)	53(24.8)	30(17.8)	4(10.0)	3(9.7)	1(11.1)
	383	214	169	40	31	9
Sex						
Female	174(45.4)	113(52.8)	61(36.1)	13(32.5)	10(32.3)	3(33.3)
Male	209(54.6)	101(47.2)	108(63.9)	27(67.5)	21(67.7)	6(66.7)
	383	214	169	40	31	9
Race						
Black	55(14.4)	33(15.4)	22(13.0)	3(7.5)	2(6.5)	1(11.1)
Hispanic	69(18.0)	34(15.9)	35(20.7)	1(2.5)	0	1(11.1)
White	207(54.1)	113(52.8)	94(55.6)	32(80.0)	26(83.9)	6(66.7)
Other	5(1.3)	2(0.9)	3(1.8)	0	0	0
Unknown	47(12.3)	32(14.9)	15(8.9)	4(10.0)	3(9.7)	1(11.1)
	383	214	169	40	31	9
Clinical Success						
Yes	222(58.0)	124(57.9)	98(58.0)	23(57.5)	17(54.8)	6(66.7)
No	53(13.8)	31(14.5)	22(13.0)	5(12.5)	3(9.7)	2(22.2)
Missing or	108(28.2)	59(27.6)	49(29.0)	12(30.0)	11(35.5)	1(11.1)
unknown	383	214	169	40	31	9
Was the patient included in the FDA subset						
Yes	383	214	169	40	31	9
No	0	0	0	0	0	0

	Alive			Death		
	Total # of pts	Cef # of pts	Con # of pts	Total # of pts	Cef # of pts	Con # of pts
Pathogen name (multiple records per patient)						
C. Perfringens	1	0	1			
Hastiforme	1	0	1			
Innocuum	1	0	1			
Bacillus sp.	1	1	0			
Propionibacterium sp.	1	1	0			
Corynebacterium sp.	1	0	1			
Jeikeium	4	1	3			
Lactobacillus sp.	1	0	1			
Bifidobacterium sp.	1	1	0			
L. Monocytogenes	1	0	1	1	0	1
Faecalis	75	41	34	3	2	1
Strep. (Alpha hemolytic)	3	0	3			
S. Viridans	2	1	1			
Strep. (beta hemolytic)	2	0	2			
Strep. (gamma hemolytic)	2	0	2			
Strep. (Group D)	9	7	2	1	1	0
S. Agalactiae	1	1	0	1	0	1
S. Intermedius	2	1	1			
Enterococcus	49	26	23	5	4	1
S. Bovis	2	2	0	1	1	0
S. Faecium	7	4	3	1	1	0
S. Salivarius	3	2	1			
S. Mitis	7	6	1	1	1	0
S. Constellatus	1	1	0			
S. Sanguis	4	1	3			
S. Avium	1	0	1			
S. Oralis	1	1	0			
Staph. sp. (MS)	1	1	0			
S. Aureus	33	10	23	6	4	2
Staph. Coagulase	24	12	12			
S. Epidermidis	26	11	15	4	2	2
S. Saprophyticus	1	1	0			
S. Hominis	2	1	1			
S. Simulans (MS)	1	0	1			
S. Haemolyticus	7	5	2	1	1	0
P. Acidilactici	1	0	1			
S. Pneumoniae	8	7	1	1	0	1
Peptostreptococcus sp.	3	3	0			
P. Anaerobius	2	2	0			
P. Micros	1	1	0			
Bacteroides sp.	4	3	1			
B. Fragilis	13	6	7			
B. Ovatus	4	3	1			
B. Vulgatus	5	5	0			
B. Thetaiotaomicron	6	2	4			
B. Distasonis	10	7	3			
B. Uniformis	5	3	2			
P. Asaccharolytica	1	1	0			
P. Intermedia	1	1	0			

	Alive			Death		
	Total # of pts	Cef # of pts	Con # of pts	Total # of pts	Cef # of pts	Con # of pts
Pathogen name (multiple records per patient)						
B. Capillosus	1	1	0			
P. Disiens	1	1	0			
P. Bivia(p+)	16	16	0			
B. Ureolyticus	1	0	1			
B. Stercoris	1	0	1			
Pseudomonas sp.	3	0	3			
P. Aeruginosa	34	19	15	2	2	0
P. Maltophilia	4	3	1	1	1	0
P. Cepacia	1	1	0			
E. Coli	32	4	28			
Citrobacter sp.	1	0	1			
C. Freundll	2	0	2			
S. Typhi	1	0	1			
K. Pneumoniae	5	1	4	2	0	2
K. Oxytoca	2	0	2			
E. Cloacae	9	2	7			
E. Aerogenes	2	0	2			
E. Intermedium	1	0	1			
P. Mirabilis	2	0	2			
H. Influenzae	1	0	1			
H. Parainfluenzae (p-)	1	1	0			
G. Vaginalis	4	3	1			
P. Multocida	1	0	1			
F. Necrophorum	1	1	0			
F. Varium	1	0	1			
Capnocytophaga sp.	1	1	0			
C. Ochracea	1	1	0			
Acinetobacter sp.	2	2	0			
A. Anitratus	5	4	1			
A. Hydrophila	1	0	1			
Diphtheroids	1	0	1			
M. Tuberculosis	1	1	0			
Candida sp.	1	0	1			
C. Albicans	1	1	0			
Mucilaginosus				1	1	0
P. Stutzeri				1	1	0
Acinetobacter sp.				1	1	0
Baumannll				1	0	1
Total	485	246	239	35	23	12

	Alive			Death		
	Total # of pts(%)	Cef # of pts(%)	Con # of pts(%)	Total # of pts(%)	Cef # of pts(%)	Con # of pts(%)
Source of microbiologic isolate (multiple records per patients)						
Blood	122(25.2)	62(25.2)	60(25.1)	18(51.4)	11(47.8)	7(58.3)
Intra-abdominal	109(22.5)	35(14.2)	74(31.0)	1(2.9)	1(4.4)	0(0)
Sputum/lung	21(4.3)	9(3.7)	12(5.0)	5(14.3)	4(17.4)	1(8.3)
Skin	2(0.4)	2(0.4)	0(0)	1(2.9)	1(4.4)	0(0)
Urine	52(10.7)	25(10.2)	27(11.3)	3(8.6)	2(8.7)	1(8.3)
Central spinal fluid	1(0.2)	0(0)	1(0.4)	1(2.9)	0(0)	1(8.3)
Other	139(28.7)	89(36.2)	50(20.9)	3(8.6)	3(13.0)	0(0.00)
Unknown	39(8.0)	24(9.8)	15(6.3)	3(8.6)	1(4.4)	2(16.7)
Total	485	246	239	35	23	12

Age	Alive			Death		
	Mean	median	range	Mean	median	range
Overall	47.77(20.62)	48	0.17-96	62.68(19.02)	65.5	1.09-88
Cef	46.78(20.89)	46	1.00-92	63.61(16.98)	67	19-88
Con	49.02(20.27)	51	0.17-96	59.45(25.84)	63	1.09-87

Sensitivity Analysis Results

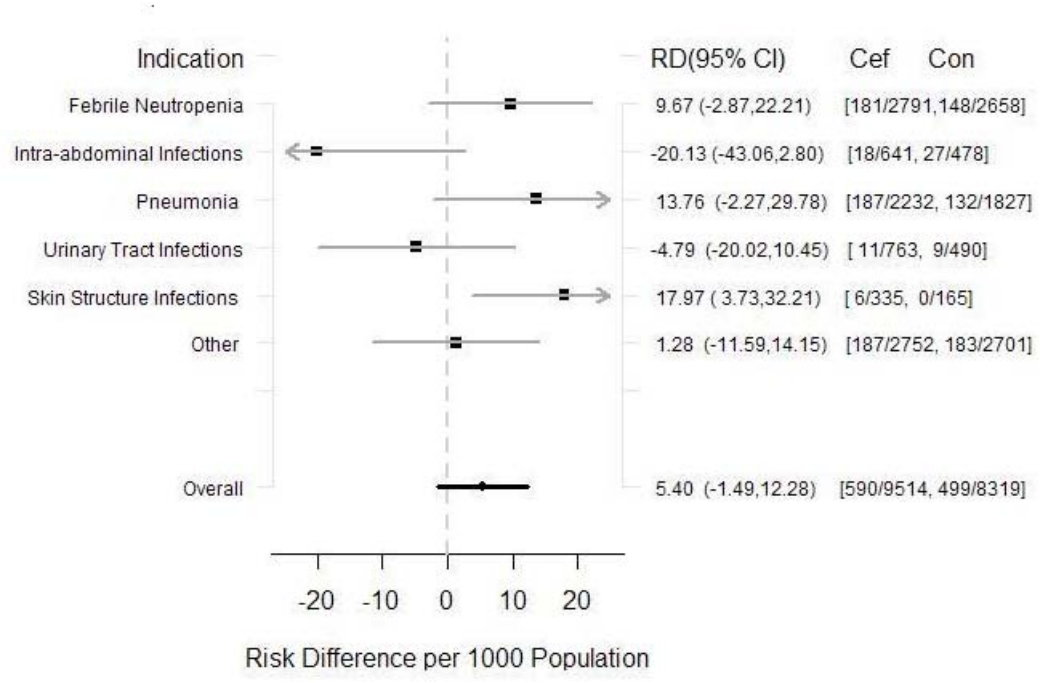


Figure 20: 30-day All-Cause Mortality Risk Difference Estimates by Indication in the Entire Safety ITT Population

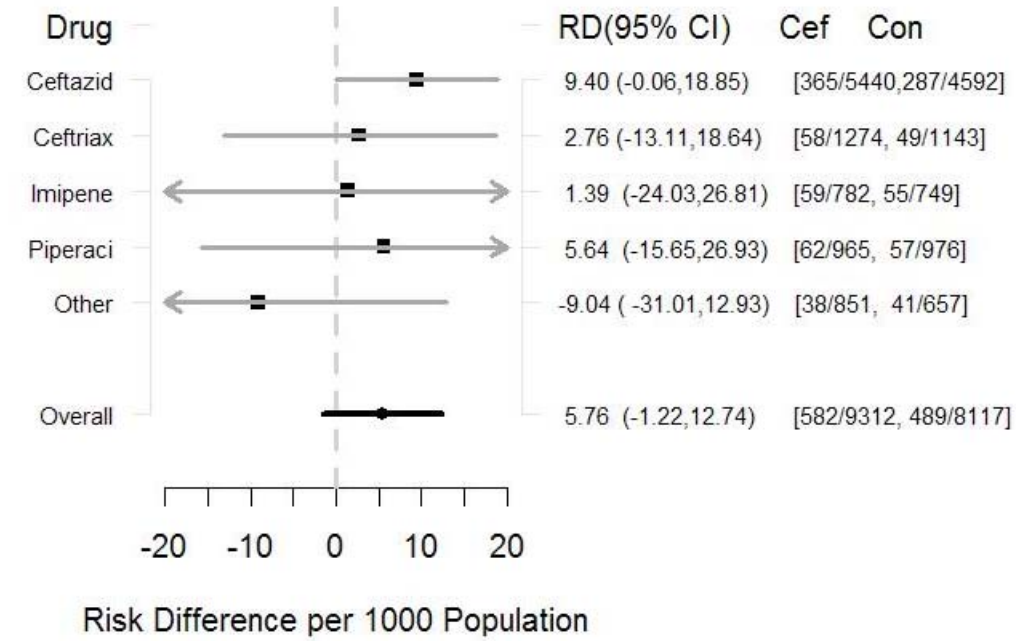


Figure 21: 30-day All-Cause Mortality Risk Difference Estimates by Comparator Drug in the Entire Safety ITT Population

Table 10: Odds ratio and 95% confidence intervals using both exact and Mantel-Haenszel methods in the safety ITT population

Subgroup factors	Exact OR (95% CI)	Mantel-Haenszel OR (95% CI)
Safety ITT population		
Overall	1.10(0.92,1.33)	1.10(0.91,1.33)
Indication		
Febrile Neutropenia	1.31(0.87,2.00)	1.31(0.87,1.99)
Intra-abdominal Infections	0.51(0.22,1.15)	0.50(0.22,1.14)
Pneumonia	1.09(0.63,1.91)	1.09(0.63,1.88)
Urinary Tract Infections	0.70(0.25,2.02)	0.71(0.26,1.91)
Skin Structure Infections	∞ (0.77, ∞)	ND (ND, ND)
Other	1.12(0.87,1.42)	1.12(0.87,1.42)
Comparator Drug		
Ceftazid	1.18(0.96,1.44)	1.18(0.96,1.44)
Ceftriax	0.95(0.53,1.71)	0.95(0.53,1.70)
Imipene	0.31(0.07,1.13)	0.31(0.08,1.17)
Piperaci	1.22(0.29,5.38)	1.23(0.31,4.82)
Other	0.61(0.13,2.79)	0.61(0.15,2.54)
Age		
0 to < 18	0.96(0.43,2.14)	0.96(0.43,2.11)
18 to < 55	1.18(0.79,1.78)	0.18(0.79,1.77)
55 to < 65	1.23(0.77,2.00)	1.23(0.77,1.97)
≥ 65	1.08(0.84,1.38)	1.08(0.84,1.38)
Gender		
Female	1.06(0.80,1.41)	1.06(0.80,1.41)
Male	1.12(0.88,1.43)	1.12(0.87,1.43)
Race		
Asian	∞ (0.02, ∞)	ND(ND, ND)
Black	0.82(0.44,1.53)	0.82(0.44,1.52)
Hispanic	0.94(0.47,1.88)	0.94(0.48,1.86)
White	1.13(0.91,1.39)	1.13(0.91,1.39)
Other	∞ (0.05, ∞)	ND(ND, ND)
Location		
US	1.04(0.81,1.34)	1.04(0.81,1.33)
Non-US	1.19(0.90,1.57)	1.19(0.90,1.57)
Pathogen recovered at baseline		
Yes	1.09(0.87,1.36)	1.09(0.87,1.36)
No	1.15(0.81,1.64)	1.15(0.81,1.64)
Pathogen isolated at baseline are susceptible study therapy		
Yes	1.07(0.79,1.45)	1.07(0.79,1.44)
No	**2.85(1.21,7.25)***	**2.66(1.14,6.21)***

*: $p<0.05$

Table 11: Exact, Mantel-Haenszel odds ratio, Mantel-Haenszel risk difference and 95% confidence intervals in the Mb ITT population

Characteristics	Exact OR (95% CI)	Mantel-Haenszel OR (95% CI)	Mantel-Haenszel RD per 1000 subjects (95% CI)
Mb ITT population			
Overall	1.11(0.89,1.38)	1.10(0.89,1.38)	5.71(-6.95,18.37)
Indication			
Febrile Neutropenia	1.44(0.70,3.04)	1.44(0.73,2.82)	27.67(-23.07,78.40)
Intra-abdominal Infections	0.41(0.14,1.10)	0.41(0.15,1.12)	-32.32(-67.99,3.35)
Pneumonia	0.88(0.48,1.62)	0.88(0.48,1.60)	-9.00(-50.58,32.58)
Urinary Tract Infections	0.70(0.25,2.01)	0.70(0.26,1.90)	-9.81(-38.74,19.12)
Skin Structure Infections	∞(0.80, ∞)	ND(ND,ND)	**22.22(4.66,39.78)***
Other	1.20(0.91,1.58)	1.20(0.91,1.58)	11.96(-6.25,30.17)
Comparator Drug			
Ceftazid	1.18(0.92,1.50)	1.18(0.92,1.50)	9.91(-4.74,24.57)
Ceftriax	0.999(0.50,2.01)	0.999(0.50,1.99)	-0.035(-34.50,34.43)
Imipene	0.45(0.09,1.76)	0.45(0.11,1.78)	-28.2(-74.97,18.49)
Piperaci	1.00(0.098,10.24)	1.00(0.13,7.67)	0(-139.70,139.70)
Other	0(0,2.39)	ND(ND,ND)	-27.70(-65.85,10.46)
Age			
0 to < 18	1.02(0.40,2.60)	1.02(0.41,2.54)	0.88(-31.55,33.30)
18 to < 55	1.03(0.61,1.76)	1.03(0.61,1.73)	0.81(-13.65,13.26)
55 to < 65	1.48(0.83,2.74)	1.48(0.82,2.68)	22.38(-9.58,54.33)
≥ 65	1.07(0.80,1.42)	1.07(0.80,1.42)	5.72(-20.10,31.54)
Gender			
Female	1.12(0.80,1.57)	1.12(0.80,1.57)	6.33(-12.54,25.20)
Male	1.08(0.81,1.46)	1.08(0.81,1.45)	1.25(-5.67,8.17)
Race			
Asian	∞(0.035, ∞)	ND(ND,ND)	142.86(-85.86,371.58)
Black	1.02(0.51,2.02)	1.02(0.52,2.00)	0.72(-25.28,26.72)
Hispanic	1.33(0.61,2.95)	1.33(0.61,2.91)	9.19(-15.31,33.69)
White	1.07(0.83,1.38)	1.07(0.83,1.38)	4.45(-12.41,21.31)
Other	∞(0.035, ∞)	ND(ND,ND)	76.10(-45.83,198.04)
Location			
US	0.99(0.75,1.31)	0.99(0.75,1.31)	-0.49(-14.16,13.18)
Non-US	1.32(0.92,1.90)	1.32(0.92,1.89)	22.17(-6.42,50.75)
Pathogen recovered at baseline			
Yes	1.09(0.87,1.36)	1.08(0.87,1.36)	4.74(-8.13,17.56)
No	3.64(0.41,97.64)	4.09(0.38,43.48)	42.39(-20.50,105.28)
Pathogen isolated at baseline are susceptible study therapy			
Yes	1.07(0.79,1.46)	1.07(0.79,1.45)	3.41(-11.1517.98)
No	**2.82(1.20,7.15)***	**2.63(1.14,6.11)***	**67.14(16.38,117.91)***

*: $p<0.05$

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/s/

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1/14/2009 02:21:20 PM
BIOMETRICS

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1/26/2009 04:57:46 PM
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1/30/2009 12:25:10 PM
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

ADDENDUM TO REVIEW COMPLETED 1/14/09

NDA Numbers:	50-679
Drug Name:	Maxipime (cefepime hydrochloride)
Indication(s):	Pneumonia Febrile neutropenia Uncomplicated and complicated urinary tract infections Uncomplicated skin and skin structure infections Complicated intra-abdominal infections
Applicant:	Bristol-Myers Squibb
Submission Date:	August 8, 2008
Date Review Completed:	April 15, 2009
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Yu-te Wu, Ph.D., M.P.H.
Statistical Team Leader:	George Rochester, Ph.D., R.A.C.
Secondary Reviewer	Charles Cooper, M.D.
Medical Division:	Division of Anti-infective and Ophthalmology Products
Clinical Team:	Peter Kim, M.D. , Clinical Reviewer Sumathi Nambiar, M.D., M.P.H., Team Leader
Project Manager:	Kyong Hyon

Keywords: Meta-analysis, mortality risk

This memo is an addendum to the original statistical review completed on 1/14/2009. Additional subgroup analyses were conducted using both trial and patient-level data.

1. Trial-level data

The FDA trial-level meta-analysis was based on data from 88 trials provided by the sponsor and other sources. In the original review, it was noted that these 88 trials included data from the 41 trials in the Yahav et al. meta-analysis and an additional 47 trials. However, the correct accounting of the trials is as follows: Of the 88 trials, 38 trials refer to 41 publications in Yahav's meta-analysis, while there are 50 additional trials that were not part of the Yahav et al. meta-analysis. The original review was based on the data of 38 trials in Yahav's meta-analysis and 50 additional trials not included in Yahav's analysis, therefore, this change does not affect all results of meta-analysis.

Below is the result for the meta-analysis based on the 50 additional trials that were not included in Yahav's analysis:

Mantel- Haenszel Risk difference per 1000 population (95% CI): -2.83 (-11.47, 5.80)

2. Patient-level data

1) US population only:
Mantel- Haenszel Risk difference per 1000 population (95% CI): 1.59(-9.21, 12.39)

2) FDA approved indications only:
Mantel- Haenszel Risk difference per 1000 population (95% CI): 3.62 (-9.09, 16.33)

3) US population and FDA approved indications only:
Mantel- Haenszel Risk difference per 1000 population (95% CI): -0.96 (-16.24, 14.32)

There was no statistically significant 30-day mortality difference between cefepime and comparator groups in the additional subgroup analyses.

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/s/

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4/22/2009 03:44:03 PM
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George Rochester
4/22/2009 08:33:14 PM
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