

SUPPLEMENTARY MATERIAL

Supplementary table 1. Percentage of susceptible *P. aeruginosa* strains from 2000 to 2017 calculated by the five methods for handling of duplicate isolates.

Antimicrobial agent	Period								
	2000-2001	2002-2003	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013	2014-2015	2016-2017
Amikacin									
All isolates	90	90	98	91	91	92	95	<u>83</u>	91
First isolate	93	95	100	96	94	92	94	<u>85</u>	92
Variation in susceptibility	90	92	97	93	<u>88</u>	93	93	<u>85</u>	94
Repeats + 7 days	93	91	98	91	91	92	93	<u>80</u>	92
Repeats + 30 days	94	96	100	96	95	92	94	<u>85</u>	92
Cefepime									
All isolates	73	62	75	69	75	71	84	72	<u>88</u>
First isolate	84	74	<u>87</u>	72	76	<u>81</u>	<u>81</u>	76	<u>87</u>
Variation in susceptibility	74	62	77	70	72	75	79	76	<u>87</u>
Repeats + 7 days	70	65	77	71	73	79	<u>82</u>	72	<u>85</u>
Repeats + 30 days	<u>82</u>	71	<u>87</u>	68	75	<u>80</u>	<u>82</u>	78	<u>86</u>
Ceftazidime									
All isolates	77	68	77	68	<u>81</u>	69	77	73	<u>87</u>
First isolate	<u>83</u>	79	90	74	<u>88</u>	74	76	77	<u>87</u>
Variation in susceptibility	72	68	<u>81</u>	70	<u>81</u>	72	74	77	<u>88</u>
Repeats + 7 days	73	69	<u>80</u>	74	<u>84</u>	72	74	74	<u>87</u>
Repeats + 30 days	<u>82</u>	77	90	71	<u>85</u>	75	78	79	<u>85</u>
Ciprofloxacin									
All isolates	<u>81</u>	72	77	40	41	39	54	51	56
First isolate	<u>88</u>	<u>86</u>	<u>82</u>	46	47	52	60	52	58
Variation in susceptibility	<u>80</u>	73	77	42	43	53	57	54	60
Repeats + 7 days	<u>81</u>	78	75	39	40	45	54	48	58
Repeats + 30 days	<u>86</u>	<u>80</u>	<u>82</u>	45	44	52	56	51	60
Gentamicin									
All isolates	69	62	71	52	41	37	42	50	61
First isolate	<u>83</u>	76	79	62	52	46	49	53	63
Variation in susceptibility	79	70	79	61	50	47	46	53	66
Repeats + 7 days	71	67	74	55	46	43	46	48	64
Repeats + 30 days	66	66	71	52	42	41	41	53	64
Imipenem									
All isolates	73	68	75	35	36	46	44	46	46
First isolate	81	83	78	42	43	65	51	45	49
Variation in susceptibility	73	70	75	37	39	60	48	47	50
Repeats + 7 days	72	77	76	37	38	57	48	41	44
Repeats + 30 days	<u>80</u>	79	78	41	44	64	49	44	48
Levofloxacin									
All isolates	79	70	78	40	44	46	55	55	55
First isolate	<u>87</u>	<u>81</u>	77	46	49	59	63	57	58
Variation in susceptibility	76	70	74	43	46	60	59	59	58
Repeats + 7 days	77	73	77	40	46	50	56	52	56
Repeats + 30 days	<u>84</u>	78	77	44	47	59	60	56	59
Meropenem									
All isolates	73	71	64	48	38	44	49	46	55

First isolate	72	<u>81</u>	74	56	44	61	55	48	61
Variation in susceptibility	70	71	67	50	40	58	52	48	60
Repeats + 7 days	69	76	64	50	37	55	50	44	55
Repeats + 30 days	71	77	74	54	44	61	52	47	61
Piperacillin/tazobactam									
All isolates	68	65	74	56	51	47	46	70	79
First isolate	<u>80</u>	76	<u>83</u>	62	65	66	51	76	<u>84</u>
Variation in susceptibility	71	65	75	53	56	59	52	74	<u>83</u>
Repeats + 7 days	70	66	75	59	53	58	48	70	<u>81</u>
Repeats + 30 days	<u>81</u>	74	<u>83</u>	61	62	66	48	77	<u>83</u>
Tobramycin									
All isolates	<u>87</u>	<u>81</u>	76	54	46	39	48	54	70
First isolate	<u>88</u>	<u>89</u>	<u>83</u>	60	53	54	54	57	71
Variation in susceptibility	<u>83</u>	<u>83</u>	79	52	49	54	50	57	72
Repeats + 7 days	<u>86</u>	<u>83</u>	76	52	47	46	47	52	72
Repeats + 30 days	<u>88</u>	<u>82</u>	<u>83</u>	60	51	54	51	56	72

In bold susceptibility $\geq 90\%$; Underlined: susceptibility $\geq 80\%$ and $< 90\%$

All isolates: including all isolates; First isolate considering only the first isolate (CLSI criteria); Variation in susceptibility: eliminating all the isolates from a patient that had the same pattern of susceptibility (EARSS criteria); Repeats + 7 days or + 30 days: eliminating isolates obtained from the same patient at day 7 or 30.

Supplementary table 2. Details of the susceptibility trends calculated by the five methods for handling of duplicate isolates

Antimicrobial	r	r ²	CI		p	β	Trend
			Lower limit	Higher limit			
Amikacin							
All isolates	0.25	0.06	-0.82	0.46	0.52	-0.18	-
First isolate	0.57	0.33	-0.95	0.12	0.11	-0.42	-
Variation in susceptibility	0.17	0.03	-0.68	0.46	0.67	-0.11	-
Repeats + 7 days	0.44	0.20	-1.08	0.31	0.23	-0.38	-
Repeats + 30 days	0.64	0.41	-0.99	0.04	0.07	-0.48	-
Cefepime							
All isolates	0.22	0.05	-0.45	0.75	0.57	0.15	-
First isolate	0.57	0.32	-1.00	0.13	0.11	-0.43	-
Variation in susceptibility	0.24	0.06	-0.42	0.75	0.54	0.16	-
Repeats + 7 days	0.10	0.01	-0.57	0.72	0.79	0.08	-
Repeats + 30 days	0.44	0.19	-0.99	0.29	0.24	-0.35	-
Ceftazidime							
All isolates	0.40	0.16	-0.49	1.43	0.29	0.47	-
First isolate	0.13	0.02	-1.16	0.86	0.74	-0.15	-
Variation in susceptibility	0.56	0.31	-0.21	1.53	0.12	0.66	-
Repeats + 7 days	0.44	0.19	-0.40	1.35	0.24	0.48	-
Repeats + 30 days	0.02	0.00	-0.97	0.94	0.97	-0.02	-
Ciprofloxacin							
All isolates	0.59	0.35	-3.89	0.39	0.10	-1.75	-
First isolate	0.70	0.48	-4.17	-0.16	0.04	-2.17	-
Variation in susceptibility	0.54	0.29	-3.30	0.54	0.13	-1.38	-
Repeats + 7 days	0.60	0.36	-3.97	0.34	0.09	-1.82	-
Repeats + 30 days	0.65	0.43	-4.00	0.07	0.06	-1.97	-
Gentamicin							
All isolates	0.52	0.27	-2.92	0.57	0.16	-1.18	-
First isolate	0.74	0.55	-3.39	-0.36	0.02	-1.88	Decreasing
Variation in susceptibility	0.64	0.41	-3.15	0.10	0.06	-1.53	-
Repeats + 7 days	0.58	0.34	-2.87	0.32	0.10	-1.28	-
Repeats + 30 days	0.45	0.20	-2.73	0.77	0.23	-0.98	-
Imipenem							
All isolates	0.66	0.43	-3.79	0.04	0.05	-1.88	-
First isolate	0.73	0.53	-4.20	-0.35	0.03	-2.28	Decreasing
Variation in susceptibility	0.60	0.36	-3.49	0.29	0.09	-1.60	-
Repeats + 7 days	0.71	0.50	-4.05	-0.22	0.03	-2.13	Decreasing
Repeats + 30 days	0.73	0.54	-4.08	-0.39	0.02	-2.23	Decreasing
Levofloxacin							
All isolates	0.57	0.33	-3.45	0.43	0.11	-1.51	-
First isolate	0.65	0.42	-3.48	0.10	0.06	-1.69	-
Variation in susceptibility	0.47	0.22	-2.62	0.66	0.20	-0.98	-
Repeats + 7 days	0.59	0.35	-3.30	0.32	0.09	-1.49	-
Repeats + 30 days	0.60	0.36	-3.36	0.28	0.09	-1.54	-
Meropenem							
All isolates	0.67	0.44	-3.02	0.00	0.05	-1.51	-
First isolate	0.65	0.43	-2.98	0.05	0.06	-1.47	-
Variation in susceptibility	0.56	0.31	-2.54	0.36	0.11	-1.09	-
Repeats + 7 days	0.65	0.42	-2.98	0.07	0.06	-1.46	-
Repeats + 30 days	0.64	0.41	-2.88	0.10	0.06	-1.39	-

Piperacillin/tazobactam							
All isolates	0.23	0.00	-2.03	1.93	0.95	-0.05	-
First isolate	0.18	0.03	-2.15	1.41	0.64	-0.37	-
Variation in susceptibility	0.15	0.02	-1.49	2.07	0.71	0.09	-
Repeats + 7 days	0.00	0.00	-1.74	1.76	0.99	0.01	-
Repeats + 30 days	0.18	0.03	-2.34	1.54	0.64	-0.40	-
Tobramycin							
All isolates	0.59	0.34	-4.10	0.44	0.10	-1.83	-
First isolate	0.68	0.46	-3.73	-0.07	<i>0.04</i>	-1.90	-
Variation in susceptibility	0.55	0.31	-3.48	0.51	0.12	-1.48	-
Repeats + 7 days	0.58	0.34	-3.98	0.43	0.10	-1.78	-
Repeats + 30 days	0.65	0.42	-3.63	0.10	0.06	-1.77	-

r: correlation coefficient; r^2 : coefficient of determination; CI: Confidence interval; β : slope

In bold $r^2 \geq 0.49$; In italic $p < 0.05$

Supplementary table 3. Antimicrobials' CFRs, for the recommended dosage regimens, calculated by the five methods for handling of duplicate isolates.

Antimicrobial agent	2000- 2001	2002- 2003	2004- 2005	2006- 2007	2008- 2009	2010- 2011	2012- 2013	2014- 2015	2016- 2017
Cefepime 2g/8h									
All isolates	79	75	81	76	77	<u>80</u>	85	73	82
First isolate	<u>86</u>	<u>87</u>	90	79	<u>80</u>	<u>85</u>	<u>84</u>	77	<u>82</u>
Variation in susceptibility	79	77	84	76	76	<u>84</u>	<u>83</u>	76	<u>83</u>
Repeats + 7 days	76	78	<u>83</u>	78	77	<u>83</u>	<u>84</u>	72	<u>81</u>
Repeats + 30 days	<u>87</u>	<u>83</u>	90	77	<u>80</u>	<u>85</u>	<u>84</u>	77	<u>82</u>
Ceftazidime 2g/8h									
All isolates	<u>89</u>	<u>85</u>	<u>89</u>	<u>84</u>	<u>89</u>	<u>85</u>	<u>87</u>	<u>84</u>	<u>89</u>
First isolate	91	90	93	<u>87</u>	91	<u>88</u>	<u>86</u>	<u>88</u>	<u>89</u>
Variation in susceptibility	<u>89</u>	<u>86</u>	90	<u>85</u>	<u>89</u>	<u>87</u>	<u>85</u>	<u>86</u>	<u>89</u>
Repeats + 7 days	<u>88</u>	<u>86</u>	<u>89</u>	<u>87</u>	<u>89</u>	<u>87</u>	<u>86</u>	<u>85</u>	<u>89</u>
Repeats + 30 days	92	<u>89</u>	93	<u>86</u>	90	<u>88</u>	<u>87</u>	<u>89</u>	<u>89</u>
Ceftazidime 2g/12h									
All isolates	79	74	79	72	77	72	75	72	77
First isolate	<u>82</u>	<u>80</u>	<u>85</u>	75	<u>81</u>	77	76	76	78
Variation in susceptibility	77	75	<u>80</u>	72	77	76	73	74	77
Repeats + 7 days	77	74	<u>80</u>	74	78	76	74	73	77
Repeats + 30 days	<u>83</u>	79	<u>85</u>	74	79	77	75	77	78
Ciprofloxacin 400mg/8h									
All isolates	71	60	70	36	35	38	47	46	50
First isolate	76	71	73	41	41	50	53	46	50
Variation in susceptibility	69	59	70	38	37	51	48	52	48
Repeats + 7 days	69	64	69	36	34	44	47	42	51
Repeats + 30 days	75	67	73	40	40	50	48	45	52
Ciprofloxacin 400mg/12h									
All isolates	64	51	64	33	30	35	39	38	38
First isolate	68	62	67	37	36	48	47	38	36
Variation in susceptibility	61	51	64	35	32	48	42	38	40
Repeats + 7 days	61	55	64	33	30	41	41	35	36

All isolates	39	38	43	32	32	29	28	4	47
First isolate	46	44	50	36	39	39	33	45	49
Variation in susceptibility	40	37	45	30	35	35	31	43	49
Repeats + 7 days	39	38	47	33	33	34	29	41	48
Repeats + 30 days	47	42	51	35	37	38	30	43	49
Piperacillin/tazobactam 4,5g/6h									
All isolates	57	56	63	49	50	45	45	60	68
First isolate	67	65	71	54	61	59	50	65	72
Variation in susceptibility	59	56	65	47	53	54	50	63	70
Repeats + 7 days	57	56	65	51	52	52	46	59	70
Repeats + 30 days	67	62	72	53	58	57	48	66	70
Tobramycin 7mg/kg/24h									
All isolates	66	59	57	39	36	33	40	44	59
First isolate	66	69	61	46	42	45	45	48	59
Variation in susceptibility	61	63	58	38	39	46	41	47	61
Repeats + 7 days	66	62	55	40	37	38	39	43	60
Repeats + 30 days	65	65	61	45	41	44	42	47	58

In bold CFR $\geq 90\%$; Underlined: CFR $\geq 80\%$ and $< 90\%$

All isolates: including all isolates; First isolate considering only the first isolate (CLSI criteria); Variation in susceptibility: eliminating all the isolates from a patient that had the same pattern of susceptibility (EARSS criteria); Repeats + 7 days or + 30 days: eliminating isolates obtained from the same patient at day 7 or 30.

Supplementary table 4. Cumulative fraction of response (CFR) trends over time obtained by the five methods for handling of duplicate isolates

Antimicrobial	r	r ²	CI		p	β	Trend
			Lower limit	Higher limit			
Cefepime							
All isolates	0.22	0.05	-0.45	0.75	0.57	0.15	-
First isolate	0.57	0.32	-1.00	0.13	0.11	-0.43	-
Variation in Susceptibility	0.24	0.06	-0.42	0.74	0.54	0.16	-
Repeats + 7 days	0.10	0.01	-0.57	0.72	0.79	0.08	-
Repeats + 30 days	0.44	0.19	-0.99	0.29	0.24	-0.35	-
Ceftazidime 2g/8h							
All isolates	0.12	0.01	-0.42	0.32	0.76	-0.05	-
First isolate	0.55	0.31	-0.53	0.08	0.12	-0.23	-
Variation in Susceptibility	0.19	0.04	-0.38	0.24	0.63	-0.07	-
Repeats + 7 days	0.15	0.02	-0.28	0.20	0.70	-0.04	-
Repeats + 30 days	0.45	0.20	-0.51	0.14	0.22	-0.18	-
Ceftazidime 2g/12h							
All isolates	0.35	0.12	-0.63	0.26	0.36	-0.18	-
First isolate	0.60	0.36	-0.80	0.07	0.09	-0.37	-
Variation in Susceptibility	0.24	0.06	-0.50	0.28	0.53	-0.11	-
Repeats + 7 days	0.26	0.07	-0.47	0.26	0.51	-0.11	-
Repeats + 30 days	0.56	0.31	-0.84	0.12	0.12	-0.36	-
Ciprofloxacin 400mg/8h							
All isolates	0.56	0.32	-3.29	0.45	0.12	-1.42	-
First isolate	0.69	0.48	-3.39	-0.11	0.04	-1.75	-
Variation in Susceptibility	0.53	0.28	-2.77	0.50	0.15	-1.13	-
Repeats + 7 days	0.59	0.34	-3.26	0.35	0.10	-1.45	-
Repeats + 30 days	0.66	0.44	-3.33	0.03	0.05	-1.65	-
Ciprofloxacin 400mg/12h							
All isolates	0.67	0.45	-3.16	-0.03	0.05	-1.59	-
First isolate	0.77	0.60	-3.31	-0.51	0.02	-1.91	Decreasing
Variation in Susceptibility	0.63	0.39	-2.72	0.15	0.07	-1.28	-
Repeats + 7 days	0.71	0.51	-3.11	-0.19	0.03	-1.65	Decreasing
Repeats + 30 days	0.76	0.57	-3.26	-0.41	0.02	-1.83	Decreasing
Gentamicin							
All isolates	0.37	0.14	-1.78	0.68	0.33	-0.55	-
First isolate	0.69	0.48	-2.39	-0.09	0.04	-1.24	-
Variation in Susceptibility	0.39	0.15	-1.72	0.62	0.30	-0.55	-
Repeats + 7 days	0.34	0.12	-1.71	0.72	0.37	-0.49	-
Repeats + 30 days	0.63	0.39	-2.32	0.12	0.07	-1.10	-
Imipenem							
All isolates	0.66	0.43	-3.79	0.04	0.05	-2.00	-
First isolate	0.73	0.53	-4.20	-0.35	0.03	-2.28	Decreasing
Variation in Susceptibility	0.60	0.36	-3.49	0.29	0.09	-1.60	-
Repeats + 7 days	0.71	0.50	-4.05	-0.22	0.03	-2.13	Decreasing
Repeats + 30 days	0.73	0.54	-4.08	-0.39	0.02	-2.23	Decreasing
Levofloxacin 500mg/12h							
All isolates	0.82	0.67	-4.33	-1.00	0.01	-2.66	Decreasing
First isolate	0.89	0.78	-4.47	-1.61	0.00	-3.04	Decreasing
Variation in Susceptibility	0.82	0.68	-3.96	-0.94	0.01	-2.45	Decreasing
Repeats + 7 days	0.83	0.69	-4.23	-1.07	0.01	-2.65	Decreasing
Repeats + 30 days	0.86	0.74	-4.41	-1.39	0.00	-2.93	Decreasing
Levofloxacin 500mg/24h							

All isolates	0.91	0.83	-4.68	-1.98	0.00	-3.33	Decreasing
First isolate	0.94	0.88	-5.04	-2.51	0.00	-3.78	Decreasing
Variation in Susceptibility	0.93	0.86	-4.49	-2.14	0.00	-3.32	Decreasing
Repeats + 7 days	0.91	0.82	-4.64	-1.90	0.00	-3.27	Decreasing
Repeats + 30 days	0.93	0.87	-4.95	-2.43	0.00	-3.69	Decreasing
Meropenem							
All isolates	0.05	0.00	-2.04	1.80	0.89	-0.12	-
First isolate	0.16	0.03	-1.93	1.35	0.69	-0.29	-
Variation in Susceptibility	0.03	0.00	-1.71	1.83	0.94	0.06	-
Repeats + 7 days	0.03	0.00	1.90	1.79	0.94	-0.06	-
Repeats + 30 days	0.12	0.14	-1.92	1.47	0.76	-0.23	-
Piperacillin/tazobactam 4.5g/6h							
All isolates	0.09	0.01	-1.18	1.45	0.82	0.13	-
First isolate	0.11	0.01	-1.34	1.06	0.79	-0.14	-
Variation in Susceptibility	0.26	0.07	-0.83	1.53	0.51	0.35	-
Repeats + 7 days	0.15	0.02	-1.00	1.40	0.71	0.20	-
Repeats + 30 days	0.11	0.13	-1.47	1.14	0.77	-0.17	-
Piperacillin/tazobactam 4.5g/8h							
All isolates	0.06	0.00	-1.01	1.15	0.89	0.07	-
First isolate	0.12	0.02	-1.08	0.82	0.75	-0.13	-
Variation in Susceptibility	0.22	0.05	-0.76	1.28	0.57	0.26	-
Repeats + 7 days	0.07	0.01	-0.98	1.14	0.86	0.08	-
Repeats + 30 days	0.18	0.03	-1.35	0.88	0.64	-0.23	-
Tobramycin							
All isolates	0.42	0.18	-2.72	0.86	0.25	-0.93	-
First isolate	0.55	0.30	-2.44	0.37	0.13	-1.03	-
Variation in Susceptibility	0.33	0.11	-2.20	0.97	0.39	-0.62	-
Repeats + 7 days	0.45	0.20	-2.67	0.75	0.23	-0.95	-
Repeats + 30 days	0.55	0.30	-2.39	0.37	0.13	-1.01	-

r: correlation coefficient; r^2 : coefficient of determination; CI: Confidence interval; β : slope

In bold $r^2 \geq 0.49$; In italic $p < 0.05$