Online Supplementary Material:
Burden of Disease and Change in Practice in Critically Ill Infants with Bronchiolitis in Australia and New Zealand 2002 to 2014

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on behalf of the Australian & New Zealand Intensive Care Society (ANZICS) Centre for Outcomes & Resource Evaluation (CORE) and the Australian & New Zealand Intensive Care Society (ANZICS) Paediatric Study Group

Methods

ANZPIC Registry. The ANZPIC Registry was created in 1997 and prospectively records demographics, physiologic variables at admission, intensive care support, diagnoses and outcomes of PICU and general ICU admissions in children <16 years of age in Australia and New Zealand. The registry captures 92-94% of all pediatric ICU admissions. Data are entered by trained ICU data collectors, and funding is provided by state governments in Australia and New Zealand. Data validation and auditing of PICUs and larger general ICUs are performed biennially.
Population-based admission rate estimates: Age-specific population data were accessed through the Australian Bureau of Statistics (http://www.abs.gov.au/AUSSTATS/abs@.nsf/second+level+view?ReadForm&prodno=3101.0&viewtitle=Australian%20Demographic%20Statistics~Jun%202012~Previous~18/12/2012&&tabname=Past%20Future%20Issues&prodno=3101.0&issue=Jun%202012&num=&view=&) and through Statistics New Zealand (http://www.stats.govt.nz/estimates-projections).
The diagnosis of bronchiolitis was based on the prospective diagnostic coding used in each patient in the ANZPIC Registry, including the principal diagnosis, the underlying diagnosis, or any of the associated diagnoses. The coding is based on the ICU discharge diagnosis by the ICU physicians.

Comorbidity definitions: The following comorbidities were defined to characterize patients with underlying disease: prematurity (< 37 weeks gestational age), chronic lung disease, underlying chronic respiratory disease other than prematurity-related chronic lung disease, congenital heart disease, chronic neurologic disease (encephalopathy; chronic central or peripheral nervous system disease), and other comorbidities (including renal disease, immunodeficiency or immunosuppression, haematological or solid organ tumors, status post bone marrow transplantation, and solid organ transplant recipients).

Cost estimates:
The ANZPIC registry data were used to estimate the costs of bronchiolitis in Australia and New Zealand, using 2014 Australian dollar costings. The costing model applied standardised prices from the National Efficient Price Determination (2014/2015) (https://www.ihpa.gov.au/sites/g/files/net636/f/publications/national_efficient_price_determination_2014-15.pdf). This model presents the activity based funding that would be provided by the Commonwealth to hospitals, based on an assumed Australian Refined Diagnosis – Related Group of Bronchiolitis with complications (E70A), weighted for time spent in intensive care, length of hospital stay and/or paediatric service. For the years 2003-2014 if data for hospital LOS were missing, imputation was used based on the median LOS for that corresponding year for general or paediatric ICU settings. As there were limited hospital LOS data available for 2002, the median LOS for 2003 was imputed for 2002.

Statistics and risk prediction models:
To assess change in risk-adjusted mortality, we recalibrated PIM2 among these patients using the linear prediction of the PIM2 model in a logistic regression model. Population-based admission rate estimates were calculated. We assessed linear trends in respiratory support over the 13-year period. In addition, trends during the 13-year study period were

assessed by comparing risk-adjusted need for invasive ventilation. We constructed a multivariate prediction model for the need for invasive ventilation. For multivariable models, all significant predictors from the univariable analyses were used. We used a backward stepwise elimination procedure to eliminate non-significant predictors based on p>0.05.

For risk prediction models, we ran a saturated mix-effects logistic regression model clustering on site. The variance of the random effect was used as a measure of unit-level variation. To avoid spurious associations between predictors that were correlated with time, we ran the saturated model with the year of admission. The model building process was undertaken using backward elimination of the covariate with the highest p-value. We selected the final model based on the lowest Akaike information criterion (AIC)[1]. The final model excluded year of admission from the model to calculate risk-adjusted change over time. A risk score for each child was calculated using the fixed effects portion of the model and the mean was calculated to estimate the average risk score of intubation. Unit level variability was reported using the predicted probability of intubation in each site for a child with the mean risk score and the site-specific random effect.

Acknowledgements

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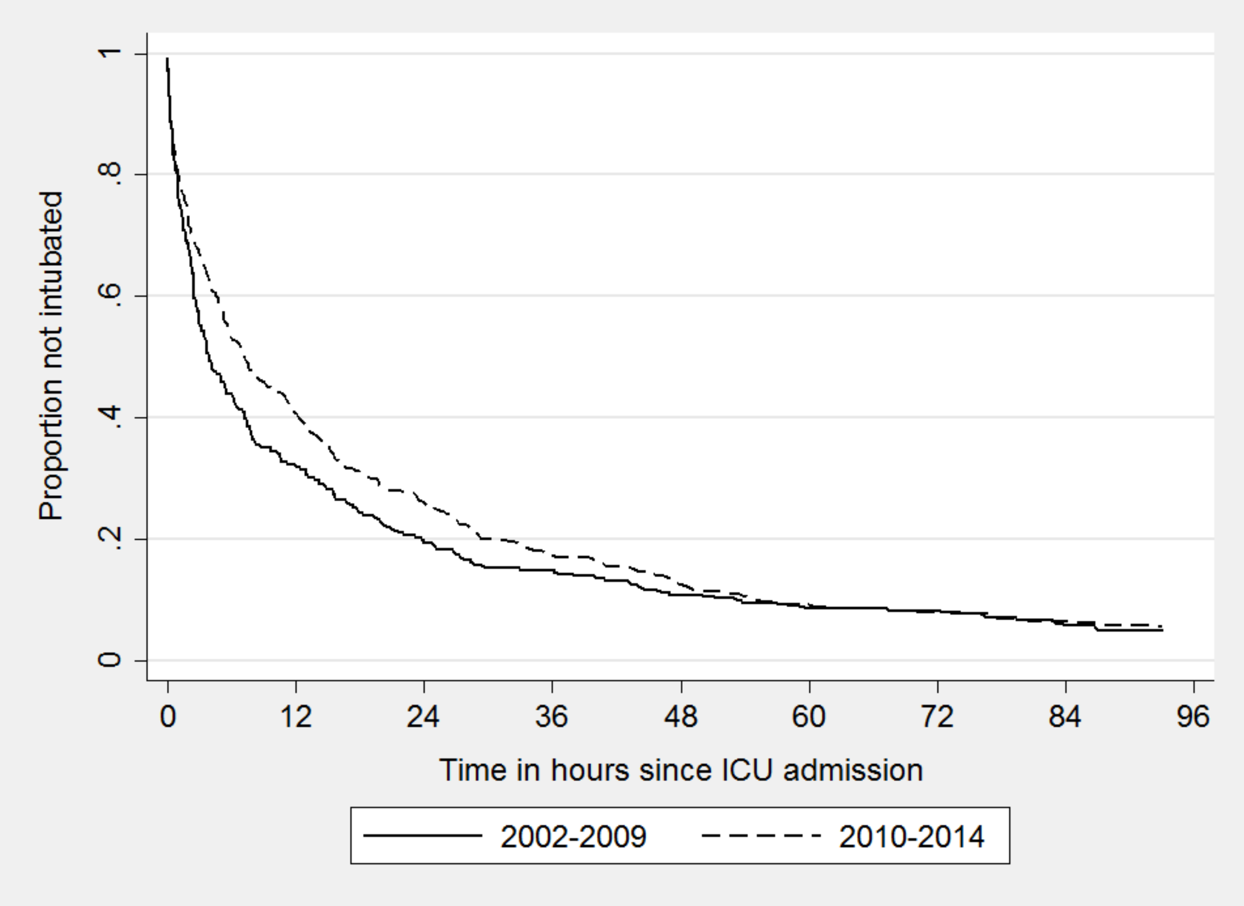
Online Supplement Figure S1: Kaplan-Meyer curves comparing time to intubation (in hours) from PICU admission in infants with bronchiolitis admitted to PICU. Only infants that were not intubated during the first hour of admission were included.



Online Supplement Table S1: Respiratory support mode and duration of respiratory support in infants with bronchiolitis admitted to ICU per year are shown for A) all ICU admissions captured in the Australian and New Zealand Paediatric Intensive Care Registry; B) admissions to Pediatric Intensive Care Units (PICUs); C) admissions to general Intensive Care Units (ICUs); D) admissions to PICUs and ICUs that had contributed to the registry for the entire study duration 2002-2014. Mechanical ventilation is defined as intubation and/or non-invasive ventilation. HFNC, High-Flow Nasal Cannulae.

Online Supplement Table S1 A: All ICUs

	Proportion of respiratory support				**Mean duration of respiratory support (hours)***				
Year	**Mechanical Ventilation****	**Invasive ventilation**	**Non-Invasive Ventilation**	**HFNC**	**Mechanical Ventilation****	**Invasive ventilation**	**Non-Invasive Ventilation**	**HFNC**	**All respiratory support**
2002	57.2%	36.6%	30.5%		108.6	125.5	53.1		62.1
2003	53.9%	30.9%	35.0%		84.1	105.1	36.7		45.4
2004	57.4%	29.2%	42.6%		102.7	147.2	37.2		58.9
2005	56.8%	29.5%	42.4%		93.9	112.4	47.8		53.4
2006	60.5%	26.9%	47.5%		94.1	134.7	43.4		56.9
2007	62.8%	26.5%	49.7%		88.0	126.1	44.0		55.3
2008	53.2%	23.5%	40.9%		87.2	119.9	44.6		46.4
2009	63.4%	25.9%	46.8%		84.7	125.7	45.3		53.7
2010	58.6%	24.5%	42.2%	24.7%	76.7	95.8	50.9	44.3	55.9
2011	62.0%	16.6%	59.3%	35.8%	68.8	109.3	41.4	35.5	55.4
2012	58.1%	20.1%	44.7%	54.7%	70.8	98.7	47.8	37.1	61.5
2013	46.6%	12.6%	38.5%	71.2%	55.6	84.1	39.8	31.6	48.4
2014	44.8%	10.8%	38.2%	72.6%	69.2	122.3	46.6	35.3	56.6
β (95% CI)	-0.01 (-0.01 to 0.00)	-0.02 (-0.02 to -0.01)	0.01 (-0.01 to 0.02)	0.06 (0.04 to 0.09)	-3.40 (-4.56 to -2.25)	-2.23 (-4.77 to 0.30)	0.09 (-0.75 to 0.92)	-2.19 (-5.82 to 1.44)	-0.03 (-0.92 to 0.86)
p (trend)	0.2311	<0.0001	0.2787	0.0001	<0.0001	0.0789	0.8260	0.1503	0.9472

* Among those children receiving this mode of respiratory support
** Defined as intubation and/or non-invasive ventilation
HFNC, High-Flow Nasal Cannulae

Online Supplement Table S1 B: PICU

	Proportion of respiratory support				Mean duration of respiratory support (hours)*				
Year	**Mechanical Ventilation****	**Invasive ventilation**	**Non-Invasive Ventilation**	**HFNC**	**Mechanical Ventilation****	**Invasive ventilation**	**Non-Invasive Ventilation**	**HFNC**	**All respiratory support**
2002	56.7%	37.2%	29.6%		109.8	125.2	53.1		62.3
2003	54.1%	32.3%	33.8%		88.0	105.7	39.8		47.6
2004	58.1%	30.4%	42.5%		106.0	148.2	39.0		61.6
2005	65.2%	34.1%	48.5%		94.6	112.4	48.2		61.7
2006	58.1%	31.1%	42.6%		105.0	137.5	42.6		61.0
2007	64.5%	29.3%	51.1%		94.2	129.0	45.0		60.8
2008	56.1%	25.1%	44.8%		90.8	126.6	42.6		50.9
2009	64.9%	27.6%	47.7%		91.2	131.2	48.1		59.2
2010	58.9%	29.6%	38.7%	30.7%	80.4	101.4	44.7	41.4	60.1
2011	58.8%	19.3%	55.4%	48.2%	83.3	120.8	46.3	35.3	66.0
2012	52.4%	21.4%	39.2%	62.1%	80.1	105.2	49.6	40.6	67.2
2013	45.5%	13.7%	37.0%	76.0%	63.9	92.0	44.6	32.1	53.4
2014	46.3%	13.0%	39.4%	74.9%	84.5	135.1	55.0	35.9	66.1
β (95% CI)	-0.01 (-0.02 to 0.00)	-0.02 (-0.02 to -0.01)	0.00 (-0.01 to 0.02)	0.07 (0.04 to 0.10)	-2.54 (-3.83 to -1.24)	-1.24 (-3.90 to 1.42)	0.44 (-0.32 to 1.19)	-1.41 (-5.12 to 2.29)	0.46 (-0.49 to 1.42)
p (trend)	0.0845	0.0000	0.4860	0.0001	0.0012	0.3264	0.2296	0.3119	0.3105

* Among those children receiving this mode of respiratory support
** Defined as intubation and/or non-invasive ventilation
HFNC, High-Flow Nasal Cannulae

Online Supplement Table S1 C: general ICUs

	Proportion of respiratory support				Mean duration of respiratory support (hours)*				
Year	Mechanical Ventilation**	Invasive ventilation	Non-Invasive Ventilation	HFNC	Mechanical Ventilation**	Invasive ventilation	Non-Invasive Ventilation	HFNC	All respiratory support
2002	64.0%	28.0%	44.0%		93.4	130.2	53.0		59.8
2003	52.9%	23.5%	41.2%		63.3	101.5	23.5		33.5
2004	48.1%	14.8%	44.4%		52.8	123.1	16.2		25.4
2005	3.8%	0.0%	3.8%		17.5	0.0	17.5		0.7
2006	70.2%	9.6%	67.3%		57.0	96.5	45.7		40.0
2007	57.1%	17.5%	45.2%		65.9	110.7	40.5		37.6
2008	43.6%	18.0%	27.8%		71.7	88.2	55.2		31.3
2009	58.8%	20.6%	44.1%		63.1	103.3	35.9		37.1
2010	57.9%	11.6%	50.9%	9.3%	67.2	59.4	62.8	68.8	45.2
2011	68.1%	11.6%	66.5%	12.9%	45.7	74.1	33.9	36.9	35.9
2012	68.5%	17.6%	54.7%	41.3%	57.9	84.2	45.5	27.4	51.0
2013	48.6%	10.5%	41.3%	62.4%	41.4	65.4	32.0	30.5	39.2
2014	42.4%	7.5%	36.3%	69.1%	44.0	89.2	32.8	34.2	42.3
β (95% CI)	0.01 (-0.02 to 0.03)	-0.01 (-0.02 to 0.00)	0.01 (-0.02 to 0.04)	0.05 (0.03 to 0.08)	-1.56 (-4.46 to 1.34)	-4.20 (-6.67 to -1.72)	0.65 (-1.75 to 3.04)	-7.55 (-21.18 to 6.07)	0.78 (-1.54 to 3.09)
p (trend)	0.6891	0.1846	0.5180	0.0010	0.2623	0.0036	0.5634	0.1759	0.4756

* Among those children receiving this mode of respiratory support

Online Supplement Table S1 D: PICUs and ICUs that had contributed to the registry for the entire study duration 2002-2014.

	Proportion of respiratory support				Mean duration of respiratory support (hours)*				
Year	**Mechanical Ventilation****	**Invasive ventilation**	**Non-Invasive Ventilation**	**HFNC**	**Mechanical Ventilation****	**Invasive ventilation**	**Non-Invasive Ventilation**	**HFNC**	**All respiratory support**
2002	57.1%	36.6%	30.5%		109.5	126.3	53.4		62.5
2003	55.8%	32.2%	36.2%		85.4	106.1	37.1		47.6
2004	58.1%	29.9%	43.0%		103.5	147.2	37.5		60.2
2005	59.9%	31.4%	44.6%		93.3	113.4	45.5		55.9
2006	60.0%	29.0%	45.7%		96.9	136.5	40.6		58.1
2007	64.5%	28.1%	51.7%		91.4	129.0	44.1		59.0
2008	53.7%	23.9%	42.4%		84.2	119.2	39.4		45.2
2009	65.9%	28.0%	48.3%		85.6	123.8	45.1		56.4
2010	62.3%	29.8%	42.5%	28.2%	74.4	97.1	40.9	38.8	57.3
2011	59.8%	18.1%	56.7%	42.7%	77.6	119.8	43.7	35.9	61.7
2012	56.0%	21.3%	42.6%	57.1%	73.7	100.2	46.8	39.5	63.8
2013	48.9%	13.4%	40.6%	75.9%	58.6	89.6	41.0	30.3	51.6
2014	49.7%	12.8%	42.5%	75.9%	76.0	129.9	49.7	33.8	63.5
β (95% CI)	0.00 (-0.01 to 0.00)	-0.02 (-0.02 to -0.01)	0.01 (0.00 to 0.02)	0.07 (0.04 to 0.09)	-3.03 (-4.23 to -1.83)	-1.73 (-4.30 to 0.85)	0.17 (-0.63 to 0.97)	-1.55 (-4.87 to 1.77)	0.29 (-0.69 to 1.27)
p (trend)	0.2526	0.0000	0.1868	0.0001	0.0002	0.1682	0.6524	0.2346	0.5223

* Among those children receiving this mode of respiratory support

Online Supplement Table S2: Estimates of population-based intubation rates in infants with bronchiolitis admitted to ICU per year. Analyses are shown for all ICU admissions captured in the Australian and New Zealand Paediatric Intensive Care Registry; admissions to Pediatric Intensive Care Units (PICUs); admissions to general Intensive Care Units (ICUs); and admissions to PICUs and ICUs that had contributed to the registry for the entire study duration 2002-2014.

	All PICUs and ICUs		**PICU**		**General ICUs**		**8 PICUs and 5 ICUs contributing to registry for the entire study duration 2002-2014**	
Year	**n**	**Population rate (per 100,000)**	**n**	**Population rate (per 100,000)**	**n**	**Population rate (per 100,000)**	**n**	**Population rate (per 100,000)**
2002	140	22.86	133	21.72	7	1.14	139	22.69
2003	98	16.06	86	14.09	12	1.97	97	15.89
2004	107	17.37	103	16.72	4	0.65	107	17.37
2005	112	17.88	112	17.88	0	0.00	111	17.72
2006	143	22.28	133	20.72	10	1.56	134	20.87
2007	140	20.72	118	17.47	22	3.26	118	17.47
2008	136	19.37	112	15.95	24	3.42	108	15.38
2009	142	19.87	114	15.95	28	3.92	124	17.35
2010	188	26.14	163	22.66	25	3.48	169	23.49
2011	146	20.50	110	15.44	36	5.05	110	15.44
2012	242	33.52	167	23.13	75	10.39	176	24.38
2013	162	21.91	114	15.42	48	6.49	119	16.09
2014	165	22.55	119	16.27	46	6.29	130	17.77
β (95% CI)	6.62 (2.01 to 11.22)	0.59 (-0.07 to 1.24)	1.99 (-1.62 to 5.60)	-0.03 (-0.55 to 0.49)	4.63 (2.73 to 6.52)	0.62 (0.35 to 0.88)	2.23 (-1.53 to 5.98)	-0.01 (-0.55 to 0.52)
p (trend)	0.0091	0.0732	0.2505	0.9020	0.0002	0.0004	0.2185	0.9603

Online Supplementary Table S3: Multivariate model to prediction of likelihood of requiring intubation and invasive ventilation in critically ill infants with bronchiolitis. Data are based on a saturated mix-effects logistic regression model clustering on site and adjusted for all variables shown in the table. Data are restricted to A) Infants that were not intubated within the first hour of ICU admission, and B) to infants treated with HFNC and not intubated during the 1st hour of ICU admission:

A) Multivariate prediction of intubation restricted to infants that were not intubated at time on ICU admission (n=8451)

	Odds Ratio	(95% CI)	β	(95% CI)	p
Age (Days/30)	0.968	(0.953 to 0.984)	-0.032	(-0.048 to -0.016)	<0.001
Interhospital transport	1.621	(1.407 to 1.868)	0.483	(0.342 to 0.625)	<0.001
Chronic Neurological Condition	1.285	(0.815 to 2.024)	0.251	(-0.204 to 0.705)	0.280
Chronic Respiratory Condition	1.531	(1.092 to 2.146)	0.426	(0.088 to 0.764)	0.014
Bronchopulmonary Dysplasia	2.035	(1.546 to 2.679)	0.711	(0.435 to 0.986)	<0.001
Congenital Heart Defect	2.168	(1.737 to 2.707)	0.774	(0.552 to 0.996)	<0.001
Prematurity	1.198	(1.006 to 1.427)	0.180	(0.006 to 0.355)	0.043
RSV	1.609	(1.394 to 1.857)	0.475	(0.332 to 0.619)	<0.001
Influenza/Parainfluenzae	1.978	(1.440 to 2.718)	0.682	(0.364 to 1.000)	<0.001
Systolic blood pressure <=70	2.916	(2.145 to 3.963)	1.070	(0.763 to 1.377)	<0.001
Base Excess	0.974	(0.950 to 0.999)	-0.026	(-0.052 to -0.001)	0.043
(Base Excess)^2	1.007	(1.005 to 1.009)	0.007	(0.005 to 0.009)	<0.001
Constant	0.968	(0.953 to 0.984)	-0.032	(-0.048 to -0.016)	<0.001

Model performance: ROC AUC=0.72 (0.70-0.73)

B) Multivariate prediction of intubation in infants not intubated on arrival and treated with High-Flow Nasal Cannulae (n=3049)

	Odds Ratio	(95% CI)	β	(95% CI)	p
Age (Days/30)	0.935	(0.902 to 0.970)	-0.067	(-0.103 to -0.031)	<0.001
Interhospital transport	0.967	(0.694 to 1.348)	-0.033	(-0.365 to 0.298)	0.845
Chronic Neurological Condition	1.054	(0.357 to 3.118)	0.053	(-1.031 to 1.137)	0.924
Chronic Respiratory Condition	1.673	(0.846 to 3.310)	0.515	(-0.167 to 1.197)	0.139
Bronchopulmonary Dysplasia	2.311	(1.228 to 4.349)	0.838	(0.206 to 1.470)	0.009
Congenital Heart Defect	3.512	(2.273 to 5.425)	1.256	(0.821 to 1.691)	<0.001
Prematurity	1.438	(0.985 to 2.098)	0.363	(-0.015 to 0.741)	0.060
RSV	1.258	(0.909 to 1.742)	0.230	(-0.096 to 0.555)	0.167
Influenza/Parainfluenzae	1.238	(0.569 to 2.692)	0.213	(-0.563 to 0.990)	0.590
Systolic blood pressure <=70	2.730	(1.329 to 5.609)	1.004	(0.284 to 1.724)	0.006
Base Excess	0.914	(0.861 to 0.972)	-0.089	(-0.150 to -0.029)	0.004
(Base Excess)^2	1.006	(1.002 to 1.010)	0.006	(0.002 to 0.010)	0.008
Constant	0.935	(0.902 to 0.970)	-0.067	(-0.103 to -0.031)	<0.001

Model performance: ROC AUC=0.74 (0.70-0.77)

Online Supplementary Table S4: Direct hospitalization costs for infants with bronchiolitis per year. Mean costs per patient, including ICU and ward costs, are shown in AU$, separately for Pediatric Intensive Care Units (PICUs) versus general ICUs. Costs are based on the standardised National Efficient Price estimates.

	Cost per patient				Total cost							Summary	
	General		PICU		General		Pediatric		Total		ICU proportion	General	PICU
Year	**Mean**	**SD**	**Mean**	**SD**	**ICU cost**	**ward cost**	**ICU cost**	**ward cost**	**ICU cost**	**ward cost**	**% total costs**	**total cost**	**total cost**
2,002	24,571	15,987	29,667	32,428	450,699	177,836	7,301,624	3,370,482	7,752,323	3,548,318	68.6	628,535	10,672,106
2,003	22,613	19,560	32,012	65,878	694,072	459,174	4,773,400	3,741,913	5,467,473	4,201,087	56.5	1,153,247	8,515,313
2,004	19,998	12,780	32,777	39,949	331,252	208,695	6,914,274	4,197,043	7,245,527	4,405,738	62.2	539,947	11,111,318
2,005	18,477	18,041	30,479	26,460	416,145	544,662	6,124,645	3,872,461	6,540,789	4,417,124	59.7	960,807	9,997,106
2,006	26,475	30,715	42,902	133,939	1,492,448	1,260,964	9,179,501	9,139,854	10,671,949	10,400,818	50.6	2,753,411	18,319,356
2,007	23,820	20,253	39,437	61,389	1,698,067	1,303,253	8,114,717	7,778,538	9,812,784	9,081,791	51.9	3,001,320	15,893,255
2,008	29,820	34,239	33,455	52,525	1,805,356	2,160,746	8,513,158	6,407,941	10,318,514	8,568,687	54.6	3,966,102	14,921,098
2,009	23,370	25,861	37,490	85,851	1,960,210	1,218,117	8,838,224	6,645,107	10,798,435	7,863,224	57.9	3,178,327	15,483,332
2,010	19,872	11,628	36,773	56,309	2,480,658	1,811,645	10,091,138	10,133,951	12,571,796	11,945,596	51.3	4,292,303	20,225,089
2,011	20,153	16,027	33,503	38,340	3,636,948	2,610,413	11,129,047	7,967,907	14,765,994	10,578,320	58.3	6,247,360	19,096,954
2,012	24,410	38,743	34,022	62,482	6,128,484	4,270,114	14,533,286	12,003,541	20,661,770	16,273,655	55.9	10,398,598	26,536,827
2,013	22,540	23,417	25,997	30,383	5,851,196	4,404,621	13,388,088	8,319,706	19,239,284	12,724,327	60.2	10,255,817	21,707,795
2,014	21,645	29,875	33,924	81,866	7,983,325	5,241,709	17,126,139	13,982,132	25,109,464	19,223,840	56.6	13,225,034	31,108,271

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