Supplement 1: Analyses of the relationship between newly occurring group A beta hemolytic streptococcal infection and subsequent changes in tic and obsessive-compulsive symptom severity. Out of the 52 Definite or Possible new GABHS infections, one infection occurred at the last patient visit. Therefore scores on the tic and OC symptom severity from the visit following an infection are available for 51 instances. The following results are based on those 51 infections for which the subsequent clinical and laboratory data were available. Considering the 51 instances of a "Definite" or "Possible" new GABHS infection, half of the time (51%, 26/51) the combined tic and OC symptom severity scores (YGTSS total tic score + CY-BOCS score) increased and half of the time (49%, 25/51) the total symptom level decreased at the time of the next encounter (See Table S3, available online). There were also 1,450 encounters when no new infection was identified. On 856 of these occasions (59%) there was no change or an improvement in the level of overall symptom severity versus 41% of the occasions when there was a "worsening" of symptoms. This difference was not significant (Chi-square(1)=2.04, p=0.15).

The average increase in the combined tic and OC symptom severity scores after a "Definite" or "Possible" new GABHS infection was 5.4 ± 4.7 which was slightly less than the scores following no new infection (5.8 ± 5.2) but this difference was not statistically significant (t(618)=0.37, p=0.71). There was a 7.4 $\pm$ 6.9 point worsening of the total symptom score if the newly diagnosed GABHS infection was treated with antibiotics and just a 4.3 $\pm$ 2.6 point increase if the newly diagnosed infection was not treated. Again the difference in worsening of the

total symptom score was not significant (t(24)=1.67, p=0.11). In the PANDAS

group, the magnitude of the increase in symptom severity scores at the next

encounter was slightly greater following a new infection (7.2 ± 6.9) than when no

new infection was detected (5.9 ± 5.4) (See Table S2, available online).

However, the difference in the mean increases of symptom severity was not

statistically significant (t(254)=0.71, p=0.48). Likewise, no significant differences

were seen in the non-PANDAS group (See Table S3, available online).

1

Table S1: Numbers of Biological Specimens and Rates of Infection

Variable	PANDAS patients	Non- PANDAS patients
Number of subjects	31	53
Total number of sera samples collected	267	380
Mean number of sera samples per subject (range)	8.6 (2 -12)	7.2 (1 -12)
Total number of throat cultures collected	650	947
Mean number of throat cultures per subject (range)	21 (5 – 27)	18 (2 – 26)
Total number of *definite* GABHS infections	7	19
Number of subjects with *definite* GABHS infections	7	17
Number of subjects with multiple *definite* GABHS infections	0	2
Maximum number of *definite* GABHS infections per subject	1	2
Total number of *possible* GABHS infections	13	13
Number of subjects with *possible* GABHS infections	10	11
Number of subjects with multiple *possible* GABHS infections	3	2
Maximum number of *possible* GABHS infections per subject	2	2
Total number of *definite* + *possible* GABHS infections[a]	20	32
Number of subjects with *definite* + *possible* GABHS infections	15	23
Number of subjects with multiple *definite* + *possible* GABHS infections	4	6
Maximum number of *definite* + *possible* GABHS infections per subject	3	3
Total number of *definite* + *possible* GABHS infections treated with antibiotics	12	9

2

Number of beta hemolytic streptococcal positive cultures, not group A (rate of positive cultures per person per year)	5 (0.09)	14 (0.17)
Number of other illnesses including pharyngitis symptoms, flu and/or upper respiratory infections with negative culture and no antibody rise (rate of other illnesses per person per year)	139 (2.52)	130 (1.59)

Note: Sixteen group A beta hemolytic streptococcal (GABHS) infections (4 in PANDAS group and 12 in non-PANDAS group) were identified based on positive throat cultures at baseline visit but were not counted as new infections as it would be impossible to evaluate date of possible acquisition of GAS without pre-baseline sera and cultures.

PANDAS = Pediatric Autoimmune Disorder Associated with Streptococcal infections

[a]Twenty positive throat cultures for group A were found in the PANDAS group and 29 positive throat cultures for group A were found in the non-PANDAS group.

Table S2: Observed vs. expected number of hits when a newly diagnosed group A beta hemolytic streptococcal infection occurred in a 22 week time window surrounding to a tic and/or OC symptom exacerbation[a]

Infection classification[b]	Number of hits[a]	Expected number of hits by chance[a]	95% CI
All subjects			
Definite GABHS infections	4 [c]	5.8	1.09, 10.24
Possible GABHS infections	4 [c]	5.8	1.09, 10.24
Definite or Possible GABHS infections	8 [c]	9.6	3.45, 15.76
PANDAS only			
Definite GABHS infections	1	1.3	0.03, 5.57
Possible GABHS infections	-	1.2	-
Definite or Possible GABHS infections	1	2.6	0.03, 5.57
Non-PANDAS			
Definite GABHS infections	3 [c]	4.5	0.62, 8.77
Possible GABHS infections	4 [c]	2.5	1.09, 10.24
Definite or Possible GABHS infections	7 [c]	7.0	2.81, 14.42

Note: CI = Confidence interval; GABHS = group A beta hemolytic streptococcal infection; PANDAS = Pediatric Autoimmune Disorder Associated with Streptococcal infections

[a]Hits = For each subject, the expected number of "hits" under the null hypothesis was calculated as the number of exacerbations experienced by the subject multiplied by the proportion of time that the subject spent two weeks prior to the detection of a new GABHS infection plus 20 weeks following the detection of a new GABHS infection. This quantity was summed across subjects in each group of subjects (PANDAS or control) to obtain the total number of "hits" that would be expected by chance alone. Please see text for the rationale for including the two week interval before a new GABHS infection was diagnosed.

[b]See text

[c]In one non-PANDAS subject, two exacerbations occurred within 2 months following definite GABHS infection and one exacerbation following a possible GABHS infection.

1

Table S3: Relationship between newly occurring Group A beta hemolytic streptococcal (GABHS) infections and subsequent changes in tic and obsessive-compulsive symptom severity.

Entire Cohort		Encounters when symptoms worsened				
GABHS Status Encounter Type	Total number of encounters	When symptoms worsened n (%)	Tic+OCD score increase mean (SD)	*Antibiotic Treatment status*	*Tic/OCD score increase mean (SD)*
Definite or possible GABHS[a]	51	26 (51)	5.4 (4.7)	*treated*	*7.4 (6.9)*
				not treated	*4.3 (2.6)*
No GABHS	1450	594 (41)	5.8 (5.2)	*NA*	*NA*
PANDAS Cases		**Encounters when symptoms worsened**			
GABHS Status Encounter Type	Total number of encounters	When symptoms worsened n (%)	Tic+OCD score increase mean (SD)	*Antibiotic Treatment status*	*Tic/OCD score increase mean (SD)*
Definite or possible GABHS[a]	20	9 (45)	7.2 (6.9)	*treated*	*9.4 (8.4)*
				not treated	*4.5 (3.7)*
No GABHS	578	247 (43)	5.9 (5.4)	*NA*	*NA*
Non-PANDAS Cases		**Encounters when symptoms worsened**			
GABHS Status Encounter Type	Total number of encounters	When symptoms worsened n (%)	Tic+OCD score increase mean (SD)	*Antiobiotic Treatment status*	*Tic/OCD score increase mean (SD)*
Definite or possible GABHS[a]	31	17 (55)	4.5 (2.7)	*treated*	*5.0 (4.2)*
				not treated	*4.3 (2.3)*
No GABHS	872	347 (40)	5.7 (5.0)	*NA*	*NA*

Note: Tic+ obsessive compulsive disorder (OCD) score (0-90) indicates the combined tic and obsessive compulsive symptom severity scores (Yale Global Tic Severity Scale (YGTSS) total tic score [0-50] + Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) score [0-40]). None of the statistical comparisons (GABHS +/- or treated +/-) were significant. PANDAS = Pediatric Autoimmune Disorders Associated with Streptococcal Infections
[a]see text for definitions of "Definite" or "Possible" infections