



Published in final edited form as:

Infect Control Hosp Epidemiol. 2014 March ; 35(3): 251–256. doi:10.1086/675281.

Are Well-child Visits a Risk Factor for Subsequent Influenza-Like-Illness Visits?

Jacob E. Simmering, MS,

Department of Pharmacy Practice and Science, University of Iowa, Iowa City, IA, USA

Linnea A. Polgreen, PhD,

Department of Pharmacy Practice and Science, University of Iowa, Iowa City, IA, USA

Joseph E. Cavanaugh, PhD, and

Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, IA, USA

Philip M. Polgreen, MD, MPH

Departments of Internal Medicine and Epidemiology, University of Iowa, Iowa City, IA, USA

Abstract

Objective—To determine if well-child visits are a risk factor for subsequent influenza-like illness (ILI) visits within a child's family.

Design—Retrospective cohort

Methods—Using data from the Medical Expenditure Panel Survey from the years 1996-2008, we identified 84,595 families. For each family, we determined those weeks in which a well-child visit or an ILI visit occurred. We identified 23,776 well-child-visit weeks and 97,250 ILI-visit weeks. We fit a logistic regression model, where the binary dependent variable indicated an ILI clinic visit in a particular week. Independent variables included binary indicators to denote a well-child visit in the concurrent week or one of the previous two weeks, the occurrence of the ILI visit during the influenza season, and the presence of children in the family in each of the age groups 0-3, 4-7, 8-17. Socioeconomic variables were also included. We also estimated the overall cost of well-child-exam-related ILI using data from 2008.

Results—We found that an ILI office visit by a family member was positively associated with a well-child visit in the same or one of the previous two weeks (OR: 1.54). This additional risk translates to potentially 778,974 excess cases of ILI per year in the US with a cost of 500 million dollars annually.

Conclusions—Our results should encourage ambulatory clinics to strictly enforce infection control recommendations. In addition, clinics could consider time-shifting of well-child visits so as not to coincide with the peak of the influenza season.

Corresponding Author: Philip M. Polgreen Division of Infectious Diseases, Department of Internal Medicine, Carver College of Medicine University of Iowa, Iowa City, IA 52242 Telephone: 319-384-6194; Fax: 319-353-5646; philip-polgreen@uiowa.edu.

Conflict of Interest: All authors report no conflicts of interest. All authors submitted the ICMJE

Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

BACKGROUND

The majority of preventive healthcare for children is administered during routine well-child visits. During these visits vaccinations are administered, screenings are performed and developmental milestones are assessed.[1] Well-child visits occur annually in children after age three and more frequently before.[1] These visits often occur in the same clinics as acute-care visits. Among younger children, respiratory infections generate a substantial number of acute care visits.[2] Unfortunately, these infections may spread in waiting and exam rooms. Routes of transmission include droplets, the hands of healthcare workers, and environmental contamination.[3-5]

To prevent the spread of infections to patients during well-child visits, several approaches are used. In addition to stressing the importance of hand hygiene and environmental cleanliness, some clinics have attempted to restrict the use of communal toys, and opened segregated well-child waiting areas.[6] However, even with these interventions, exam rooms are usually not segregated. In addition, hand-hygiene compliance and environmental cleaning are routinely not optimal.[7] Overcrowding during respiratory-virus season may further increase the risk of transmission.

Knowing the level and timing of elevated risk during ambulatory care may allow rearranging or rescheduling of well-child visits so they do not occur during the peak of the influenza season. However, little information exists about the scale of the problem in pediatric offices. The purpose of this paper is to determine if well-child visits are a risk factor for subsequent influenza-like illness (ILI) visits within the child's family. We also estimate the cost of these subsequent infections on a national level.

METHODS

The Agency for Healthcare Research and Quality's Medical Expenditure Panel Survey (MEPS) is a longitudinal, nationally-representative sample of the US population. Primary focus areas are healthcare utilization, expenditures and health-related attitudes.[8] For our analysis, we used the demographic, office-based, emergency room and outpatient event files from years 1996 to 2008. This reflects the entirety of the non-inpatient medical care for each subject.

We extracted ILI visits using International Classification of Diseases, 9th Revision (ICD-9) codes from the pooled outpatient, office-based and emergency-department visit records. Visits were labeled as ILI if they included at least one of the 16 ICD-9 codes listed in Marsden-Haug, shown here in Table 1.[9] Next, we extracted well-child visits based on two criteria: if the records included ICD-9 codes previously used for well-child visit studies[10] or if the primary reason for the visit was “immunizations or shots” or “well-child exam”. We focused on well-child visits occurring in patients under the age of 6 to focus on child health prior to enrollment in elementary school.

We used the MEPS data to create family units. MEPS provides a dwelling unit ID and subclassifies the dwelling unit into families. Combining the unique dwelling unit ID and the family ID generates a unique key for each family. Within these families we created an

indicator variable for each week that a well-child visit occurred for a child under the age of 6. We also created an indicator variable for each week that an ILI occurred for any family member. Because MEPS panels run for 2 years, each family had up to 104 weeks of observation. Given the 84,595 families under observation, this translates to 8,053,344 overall records.

To determine if well-child visits are a risk factor for subsequent ILI visits, we used survey weighted logistic regression. For most of our analyses, the unit of analysis was the family. In our model, an ILI visit in a particular week was the dependent variable. Independent variables included an indicator for the well-child visit risk-window, defined as 1 if there was a well-child visit in same or one of the previous two weeks. The consideration of the prior two weeks accounts for the delay in presentation of ILI. To control for socio-demographic factors, we included the race and education for the MEPS reference, where the reference person is the person who rents or owns the dwelling unit for the family. To account for access to care, we included whether the reference person had private, public or no insurance. Family income was converted to percentage of the poverty level and coded as one of 5 levels: poor (income > 100% poverty line), near poor (100% to 124%), low income (125% to 199%), middle income (200% to 399%) and high income (> 400%). To control for the effect of other children in the family unit, we also included a series of indicator variables to represent the presence of children aged 0-3 years, 4-7 years and 8-17 years. We defined these cutoffs empirically. Finally, we included a dummy variable representing whether the ILI visit occurred during the influenza season. We defined the influenza season as the months of December, January and February. Analysis was done using the Survey package and R 3.02.

As a further check of association, we explored the existence of an interaction between the influenza season and the well-child visits. If infections are acquired during well-child care, we would expect the effect of well-child visits on subsequent ILI visits to be elevated during the influenza season. Additionally, as a sensitivity analysis, we assessed the effect of the chosen risk-window for the well-child visit by shortening it by a week to include only the same or the previous week as the ILI visit. We also modified the definition of well-child visit to be only those visits in children aged 3 and under.

To evaluate the cost of well-child-related ILI, we used the MEPS data for 2008 to obtain an estimate that is adjusted by the MPES survey-sampling weights. Using the model without interactions, we calculated the difference in risk of an ILI visit for every family with a well-child visit compared to the counterfactual of no well-child visit. We estimated the total increase in risk during the well-child visit risk-window with all covariates except for the well-child indicator held constant. Using the MEPS covariates allows us to make more accurate estimates of the total increase in risk than, for example, considering the effect of a well-child visit with the other covariates set at their mean/modal values. The resulting estimate is more reflective of the total national burden. We estimated the average increased risk using a survey weight adjusted mean of the computed increased risk for each family. Using the total annual number of cases and economic burden of outpatient influenza reported by Molinari and colleagues, we estimate the mean cost of a case of outpatient

influenza as \$642.06.[11] This estimate reflects direct medical costs and indirect costs such as lost work.

RESULTS

During our study period of 13 years, we followed 84,595 families. We found 23,776 family-weeks with a well-child visit in children under age six. We also detected 97,520 family-weeks with an ILI visit among family members of any age.

The results from our model exploring the risk factors for ILI visits at a family level are shown in Table 2. We found that a lack of insurance was associated with reduced odds of having ILI office visits. Families on public insurance were more likely to have ILI office visit than their privately insured peers. In terms of race, we found that whites were the most likely group to have an ILI visit. Higher income and higher education levels were also positively associated with ILI visits. Families with young children were more likely to have an ILI visit. As expected, the influenza season was associated with increased risk for ILI.

Finally, we found that even when controlling for all of the preceding factors, the occurrence of an ILI office visit by a family member was strongly associated with a well-child visit in the same or either of the two previous weeks. In fact, the odds of an ILI visit for a family with a well-child visit in the same or either of the prior two weeks were 1.54 ($p < 0.0001$) times that of a family without a well-child visit in this time period.

The inclusion of the interaction term between the influenza season and the well-child visit indicator slightly attenuated the main effect of the well-child visit (OR 1.46, $p < 0.0001$). This is because the estimate in the additive model reflects the average burden over the year. If a well-child visit was additively more risky during the influenza season, that relationship would be captured by the influenza season variable. If a well-child office visit elevates the log odds of an ILI visit to a greater extent during the influenza season, we would expect the interaction term to be positive. This could be the case if the influenza season created greater ILI volume in the clinic, thereby increasing the exposure during a well-child office visit. The interaction between the well-child and influenza season indicator variables was significant and positive (OR 1.18, $p = 0.0114$). This suggests that the effect of a well-child visit on increasing the risk for subsequent ILI is more pronounced during the influenza season.

Neither of our two sensitivity analyses alter our results. If we shorten the risk window by one week, the OR remains practically constant at 1.56 ($p < 0.0001$). Likewise, if we restrict to only the 26,786 well-child visits in patients aged 3 or younger we arrive at an OR of 1.50 ($p < 0.0001$). In comparison, defining well-child office patients to be 5 or younger and including the same and prior two weeks in the risk window yields the OR of 1.54 ($p < 0.0001$).

Using the family characteristics and sampling design in MEPS for 2008 and without considering the interaction between influenza season and well-child office visits, we arrive at an average 3.17 percentage points (interquartile range: 2.44 – 3.91) increase in the probability of an ILI office visit in the week of or two weeks following a well-child visit. When the sample weights are applied, this reflects a potential excess of 778,974 ILI office

visits. Using \$642.06 as the estimated economic burden of outpatient influenza, we arrive at an annual cost of \$500,147,992. Repeating this computation using the model with an interaction term yields a comparable increase in the probability of an ILI office visit (3.12%, IQR 2.13 – 3.72). Using the estimate with the interaction and the sampling weights as before, we estimate 766,151 additional ILI office visits and \$491,914,592 annual costs.

DISCUSSION

Our results demonstrate that well-child visits are associated with ILI visits during the week of and two weeks following a well-child visit. Specifically, we find a 3.17 percentage point increase in the probability of an ILI visit based on a well-child visit in the concurrent week or either of the previous two weeks. Although this risk is relatively small, the number of well-child visits on a national level is not. We estimate 778,974 potentially-avoidable ILI visits for a total economic burden of over half a billion dollars in 2008. Given that actual provider-based visits measure only a fraction of ILI episodes, this may substantially underestimate the potential risk of well-child visits.

Children and their family members attending well-child visits are certainly at risk for acquiring infections. However, it has been much harder to document the risk factors for infections from ambulatory exposures than hospital-associated infections. Exposures to some diseases in ambulatory clinics are easier to diagnose based on ease of transmission, clinical presentation and how common the infections are in general. For example, in the U.S. during some outbreaks, a substantial percentage of measles cases were linked to exposures in ambulatory care environments.[12-13] Transmission of tuberculosis has also been linked to exposures in pediatric clinics.[14-15] However, exposures and transmission of infections that occur commonly in the community are not reported, and this may be due to the difficulty of attributing exposure to office visits.[5] One study of 127 children was designed to determine the risk of acquiring an infection in the week following a pediatric office visit. This study did not detect an increased risk following the visit.[16] Another study of 304 children, 137 of whom had an emergency department visit, did not find an increased risk of infection.[17] A similar larger study of emergency department visits among elderly residents of long-term-care facilities (1269 participants, 424 of whom visited the emergency department) found that a visit was associated with a 3-fold increase in the risk of a subsequent acute infection.[18]

The unique design of the MEPS enabled us to do a much larger investigation than has been done previously. We were able to capture important variables that may explain access to care, the timing of the visits, and most importantly, the potential for capturing possible ILI visits among family members, not just the patients attending the well-child visits. In addition, we were able to capture visits that occur in multiple settings across healthcare and payer systems.

Our results stress the importance of infection-control in ambulatory settings. Infection-prevention- and-control guidelines for pediatric clinics exist, and these highlight a number of interventions that may be undertaken. Many policies focus on reducing the transmission of respiratory infections. These include improving environmental cleaning, respiratory hygiene

and cough etiquette, and hand-hygiene compliance.[3-5] The last two interventions can be practiced by both patients and their family members as well as healthcare workers to reduce risk. In fact, the most effective approach to infection control in ambulatory settings involves the sharing and coordination of information at an early stage. The American Academy of Pediatrics Committee on Infectious Diseases states that “Infection prevention and control should start at the time an ambulatory visit is scheduled and is important in every patient encounter.”[3] We would argue that this approach should be taken even further so that infection control starts before the well-child visit is scheduled.

Currently, the timing of well-child visits does not exploit information that could decrease the risk of respiratory viruses. Well-child visits are often based on patients’ birthdays as a convenient way to ensure complete and timely vaccinations. It may be possible that changing scheduling by a few weeks, based on local influenza patterns, may decrease exposures and secondary illnesses for both children attending well-child visits and their family members. An alternative would be to decrease the number of well-child visits scheduled during the peak “influenza season.” This approach may make staffing clinics easier: the upswing in activity due to the respiratory virus season often provides greater demand for acute care services. However, any potential benefits from shifting well child visits to avoid the peak of influenza season need to be weighed against possible disruptions in routine vaccination scheduling. Thus, we think that before any changes to well-child scheduling are even considered, reinforcing and implementing currently recommended clinic-based infection control guidelines should be most vigorously pursued. The well-child visits are not generating additional ILI cases, it is the possible exposures that occur -- many of which could be mitigated via better infection control practices -- that are generating the additional ILI cases. There are several limitations to our study. First, we captured ILI visits using the administrative codes provided by MEPS. These diagnoses were not based on microbiological data (e.g., cultures, chart reviews). Also, because the MEPS data only includes the first three digits of the ICD-9 codes, it is possible that we are misclassifying some events. However, the first three digits provide clinically meaningful categories that are likely specific enough for this study.

Second, we do not know which family members were exposed at a visit or the extent of the exposure. However, we did observe an increase in risk for ILI visits following well-child visits for the patient. This lends support to the estimates obtained considering the entire family. Third, the analysis did not consider influenza vaccination habits among the family. However, vaccination for all children 6 months to 4 years was recommended for the 2007-2008 influenza season and for all children with the 2008-2009 season. Children presenting at well-child visits are potentially likely to be vaccinated or offered vaccination against the influenza. This would tend to bias our findings towards the null of no association.

Fourth, it is possible that the relationship that we found between well-child visits and ILI is caused by a common temporal relationship with an omitted variable such as the school year. However, this is not likely: ILI visits are highly seasonal, but well-child visits are not. We also considered multiple alternative definitions of the influenza season, but these alternative definitions yielded essentially the same results (data not shown).

Finally, our findings may be based on some omitted variables not captured by MEPS that are associated with both well-child visits and ILI visits, like care-seeking behavior. However, we included the variables that were available in MEPS that could be associated with care seeking (parents' education and insurance status, for example). Note that many of these variables were statistically significant, but the estimated odds ratios for many of these variables were relatively small compared to that of the well-child visit variable, the focus of our study (See Table 2). In addition, when we repeat the analysis but replace the ILI office visit with an outpatient office visit for a sprain or strain, we find no significant increase in risk based on a well-child visit in the same week or either of the previous two weeks (OR 1.18, 95% CI 0.94 – 1.45). We found no causal relationship between well-child care and these injuries except for differences in care seeking preferences between families with and without well-child visits. The lack of a significant increase in risk of a sprain or strain in the weeks following well-child visits, in addition to the relatively small odds ratios for the other included variables, suggests that our finding is unlikely to be the result of care-seeking behavior by families who schedule and attend well-child visits.

Despite our limitations, we provide some of the first evidence for what many have suspected: ambulatory exposures are a potential risk factor for respiratory infections. We believe that attendance at well-child visits is critically important for preventing infections through vaccination and the benefits far outweigh the risks. Nonetheless, our results stress the importance of improving compliance with current infection-control guidelines for ambulatory settings, not just for well-child visits, but for all office visits.

Acknowledgments

none

Funding: This work was supported in part by a grant from the National Institutes of Health [K01AI75089 to P.M.P.]; and a KL2 from the University of Iowa Institute for Clinical and Translational Science [to L.A.P.].

REFERENCES

1. Bright Futures/American Academy of Pediatrics. [April 9, 2012] Recommendations for Preventive Pediatric Health Care (Periodicity Schedule). <http://practice.aap.org/content.aspx?aid=1599>.
2. Schappert SM, Burt CW. Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 2001-02. *Vital Health Statistics*. 2006; 13:1–66.
3. American Academy of Pediatrics, Committee on Infectious Diseases. Infection prevention and control in pediatric ambulatory settings. *Pediatrics*. 2007; 120:650–665. [PubMed: 17766540]
4. Posfay-Barbe KM, Zerr DM, Pittet D. Infection-control in paediatrics. *Lancet Infect Dis*. 2008; 8:19–31. [PubMed: 18156087]
5. Canadian Paediatric Society. Position Paper 2008-03: Infection-control in paediatric office settings. *Paediatr Child Health* 2008. 13:408–435.
6. Posfay-Barbe KM, Zerr DM, Pittet D. Infection-control in paediatrics. *Lancet Infect Dis*. 2008; 8:19–31. [PubMed: 18156087]
7. Turnberg W, Daniell W, Seixas N, et al. Appraisal of recommended respiratory infection control practices in primary care and emergency department settings. *Am J Infect Control*. 2008; 36:268–275. [PubMed: 18455047]

8. U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality. [April 9, 2012] MEPS: Medical Expenditure Panel Survey. Available at: <http://meps.ahrq.gov/mepsweb/>.
9. Marsden-Haug N, Foster VB, Gould PL, Elbert E, Wang H, Pavlin JA. Code-based syndromic surveillance for influenza-like illness by International Classification of Diseases, Ninth Revision. *Emerg Infect Dis.* 2007; 13:207–216. [PubMed: 17479881]
10. Cohen D, Coco A. Trends in well-child visits to family physicians by children younger than 2 years of age. *Ann Fam Med.* 2010; 8:245–248. [PubMed: 20458108]
11. Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine.* 2007; 25:5086–5096. [PubMed: 17544181]
12. Herwaldt LA, Smith SD, Carter CD. Infection-control in the outpatient setting. *Infect Control Hosp Epidemiol.* 1998; 19:41–74. [PubMed: 9475349]
13. Goodman RA, Solomon SL. Transmission of infectious diseases in outpatient health care settings. *JAMA.* 1991; 265:2377–2381. [PubMed: 2016835]
14. Askew GL, Finelli L, Hutton M, et al. Mycobacterium tuberculosis transmission from a pediatrician to patients. *Pediatrics.* 1997; 100:19–23. [PubMed: 9200355]
15. Moore M, Schulte J, Valway SE, et al. Evaluation of transmission of Mycobacterium tuberculosis in a pediatric setting. *J Pediatr.* 1998; 133:108–12. [PubMed: 9672521]
16. Lobovits AM, Freeman J, Goldmann DA, McIntosh K. Risk of illness after exposure to a pediatric office. *N Engl J Med.* 1985; 313:425–428. [PubMed: 4022069]
17. Quach C, Moore D, Ducharme F, Chalut D. Do pediatric emergency departments pose a risk of infection? *BMC Pediatr.* 2011; 11:2. [PubMed: 21214927]
18. Quach C, McArthur M, McGeer A, Li L, Simor A, Dionne M, Lévesque E, Tremblay L. Risk of infection following a visit to the emergency department: a cohort study. *CMAJ.* 2012; 184:E232–E239. [PubMed: 22271915]

Table 1

ICD-9 codes used to define ILI Code Condition

079 Viral Infection Symptoms
460 Common Cold
462 Acute Pharyngitis
464 Acute Laryngitis and Tracheitis
465 Acute Upper Respiratory Infection
466 Acute Bronchitis and Bronchiolitis
478 Other Diseases of the Upper Respiratory Tract
480 Viral Pneumonia
484 Pneumonia in Infectious Diseases
485 Bronchopneumonia
486 Pneumonia (Unspecified organism)
487 Influenza
490 Bronchitis
780 General Symptoms (e.g., fever, fatigue)
784 Head and Neck Symptoms (e.g., headache, throat pain)
786 Respiratory Symptoms Not Specified Elsewhere

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Risk Factors for ILI Office Visit: Multivariate Logistic Regression Results, Dependent Variable: ILI Office Visit*

Independent Variable	Adjusted Odds Ratio	Confidence Interval	Wald Statistic	p-value
Race:				
Black vs White	0.62	0.58 – 0.66	-14.31	<0.0001
Asian vs White	0.70	0.64 – 0.77	-7.59	<0.0001
Other vs White	0.84	0.75 – 0.95	-2.72	0.0068
Insurance:				
Only Public vs Any Private	1.22	1.15 – 1.29	6.71	<0.0001
No Insurance vs Any Private	0.58	0.54 – 0.63	-14.61	<0.0001
Household Income:				
Near Poor vs Poor	1.05	0.96 – 1.14	1.09	0.2778
Low Income vs Poor	1.02	0.95 – 1.09	0.44	0.6578
Middle Income vs Poor	1.14	1.07 – 1.23	3.78	0.0002
High Income vs Poor	1.21	1.12 – 1.31	4.86	<0.0001
Reference Person Education:				
GED/High School vs No Degree	1.02	0.97 – 1.08	0.87	0.3854
College/College+ vs No Degree	1.08	1.02 – 1.15	2.50	0.0127
Other Education vs No Degree	1.08	1.00 – 1.17	1.88	0.0603
Presence of Children:				
Aged 0-3	1.80	1.72 – 1.89	23.62	<0.0001
Aged 4-7	1.55	1.48 – 1.62	19.47	<0.0001
Aged 8-17	1.38	1.32 – 1.44	15.72	<0.0001
Influenza Season	1.47	1.37 – 1.44	29.53	<0.0001
Well-child visit in same or previous				
2 weeks	1.54	1.43 – 1.66	11.69	<0.0001

* Data are taken from the Medical Expenditure Panel Survey, 1996-2008; N = 84,595 families.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3

Risk Factors for ILI Office Visit: Multivariate Logistic Regression Results with Interaction Between Well-Child Visit Risk Window and Influenza Season *

Independent Variable	Adjusted Odds Ratio	Confidence Interval	Wald Statistic	p-value
Race:				
Black vs White	0.62	0.58, 0.66	-14.31	<0.0001
Asian vs White	0.70	0.64, 0.77	-7.59	<0.0001
Other vs White	0.84	0.75, 0.95	-2.72	0.0067
Insurance:				
Only Public vs Any Private	1.22	1.15, 1.29	6.71	<0.0001
No Insurance vs Any Private	0.58	0.54, 0.63	-14.61	<0.0001
Household Income:				
Near Poor vs Poor	1.05	0.96, 1.14	1.09	0.2782
Low Income vs Poor	1.02	0.95, 1.09	0.44	0.6591
Middle Income vs Poor	1.14	1.07, 1.23	3.78	0.0002
High Income vs Poor	1.21	1.12, 1.31	4.86	<0.0001
Reference Person Education:				
GED/High School vs No Degree	1.02	0.97, 1.08	0.87	0.3855
College/College+ vs No Degree	1.08	1.02, 1.15	2.50	0.0128
Other Education vs No Degree	1.08	1.00, 1.17	1.88	0.0603
Presence of Children:				
Aged 0-3	1.80	1.72, 1.89	23.61	<0.0001
Aged 4-7	1.55	1.48, 1.62	19.48	<0.0001
Aged 8-17	1.38	1.33, 1.44	15.73	<0.0001
Influenza Season	1.40	1.37, 1.43	28.87	<0.0001
Well-child visit in same or previous 2 weeks	1.46	1.35, 1.59	9.07	<0.0001
Well-child visit/Influenza season interaction	1.18	1.04, 1.35	2.54	0.0114

* Data are taken from the Medical Expenditure Panel Survey, 1996-2008; N = 84,595 families.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript