Pertussis Immunization in Infancy and Adolescent Asthma Medication

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KEY WORDS

asthma, immunization, national cohort, medication, pertussis

ABBREVIATIONS

CI—confidence interval

DTaP—diphtheria-tetanus-acellular pertussis

ICS—inhaled corticosteroid

ITT—intention-to-treat

LTRA—leukotriene antagonist

OR—odds ratio

PP—per-protocol

SMBR—Swedish Medical Birth Register

Th2—T-helper cell type 2

wP—whole-cell pertussis

Dr Vogt performed the literature review, conceptualized and designed the study, processed the register data, performed certain data analyses, interpreted the data, and drafted the initial manuscript; Dr Bråbäck performed the literature review, conceptualized and designed the study, interpreted the data, and critically revised the manuscript; Ms Kling and Dr Grünewald conceptualized and designed the study, performed most of the data analyses, interpreted the data, and critically revised the manuscript; and Dr Nilsson performed the literature review, conceptualized and designed the study, interpreted the data, and critically revised the manuscript. All authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Childhood immunization might contribute to an increase in asthma prevalence. Previous studies have been contradictory, and many lack sufficiently large control groups of nonimmunized children.

WHAT THIS STUDY ADDS: Pertussis immunization in infancy does not increase the risk of asthma medication in adolescents. Our study presents convincing evidence that pertussis immunization in early childhood can be considered safe with respect to long-term development of asthma.

abstract

BACKGROUND AND OBJECTIVES: Childhood immunization may influence the development of asthma, possibly due to lack of infections or a shift in the T-helper cell type 1/T-helper cell type 2/regulatory T cells balance. We therefore investigated whether pertussis immunization in infancy is associated with asthma medication in adolescence.

METHODS: After 14 years of no general pertussis vaccination, almost 82 000 Swedish children were immunized for pertussis in a vaccination trial between June 1, 1993, and June 30, 1994. In a follow-up analysis of almost 80 000 children, their data were compared with those of ~100 000 nonvaccinated children, born during a 5-month period before and a 7-month period after the vaccination trial. Data for the main outcome variable (ie, dispensed prescribed asthma medication for each individual in the cohort during 2008–2010) were obtained from the national prescription database. Multivariate regression models were used to calculate the effect size of vaccination on dispensed asthma medication (odds ratios [OR], 95% confidence intervals [CI]). Approaches similar to intention-to-treat and per-protocol methods were used.

RESULTS: The prevalence rates of various asthma medications for study patients at 15 years of age differed between 4.6% and 7.0%. The crude ORs for any asthma medication and antiinflammatory treatment in pertussis-vaccinated children after intention-to-treat analysis were 0.97 (95% CI: 0.93–1.00) and 0.94 (95% CI: 0.90–0.98), respectively. Corresponding adjusted ORs were 0.99 (95% CI: 0.95–1.03) and 0.97 (95% CI: 0.92–1.01). Similar ORs were found after per-protocol analysis.

CONCLUSIONS: Pertussis immunization in infancy does not increase the risk of asthma medication use in adolescents. Our study presents evidence that pertussis immunization in early childhood can be considered safe with respect to long-term development of asthma. *Pediatrics* 2014;134:721–728

The growing prevalence of asthma in recent decades, especially in affluent countries, has led to a lively debate. Different causal explanations have been discussed, all suggesting a shift in immune regulation and response that results in increased susceptibility to asthma and allergic diseases.¹ The so-called “hygiene hypothesis” suggests that a lack of infections during early infancy might increase the risk of asthma and allergic diseases because of lower exposure to microorganisms.² As a consequence of the hygiene hypothesis and the absence of certain infectious diseases, common childhood vaccinations have been suspected as a possible cause of the increase in asthma and allergic diseases in affluent countries.³

Immunization might promote allergy, either by skewing the immune system toward a T-helper cell type 2 (Th2) cytokine pattern or through indirect promotion of allergy by hindering T-helper cell type 1-associated infections, thereby strengthening the Th2-type arm of the immune system. Pertussis toxoid is a well-known adjuvant for IgE sensitization in animals.⁴ Whole-cell pertussis (wP) vaccine stimulates the adaptive immune system in a T-helper cell type 1 cytokine pattern; acellular pertussis vaccines, mostly in use today, more commonly produce a Th2-type cytokine response.⁵

Several investigations have focused on the role of pertussis or combined diphtheria-pertussis-tetanus immunization, with contradictory results,^{3,6–14} including the only randomized controlled trial published thus far.¹⁵ In most of these studies, a wP vaccine was used. Although there is no convincing evidence for the association between early infancy immunization against pertussis and asthma or atopic disease later in childhood,¹⁶ it seems too early to discard the contributory role vaccines may have in the development of allergic diseases.^{17,18} Methodologic in-

congruence between different studies has led to calls for further investigations on a larger scale that are well controlled for possible bias.¹⁹ This research seems particularly important as parental fear concerning vaccine safety and the risk of developing other diseases have been recognized as major obstacles to the immunization of infants.²⁰

The goal of the present study was to analyze data on dispensed antiasthmatic medication in teenagers in relation to pertussis immunization in infancy to collect further evidence of whether pertussis vaccination contributes to a higher risk of asthma disease later in life.

METHODS

Study Population and Data Linkage

Our study population is based on >80 000 former participants in an efficacy trial, previously described in detail,²¹ of 3 acellular pertussis vaccines compared with a wP vaccine. As a control group, we included 98 475 children born during a 5-month period before, and a 7-month period after, the vaccination trial with data from the Swedish Medical Birth Register (SMBR) and who were not offered pertussis immunization (at that time, there had been no general pertussis vaccination in Sweden for 14 years). During the period of the vaccination trial, 21 485 children were not vaccinated for various reasons (Fig 1A) but are included in some of our analyses. The total number of nonvaccinated children is based on subjects born during the observation period whose data were available from the SMBR.

Briefly, infants born between June 1, 1993, and May 31, 1994, in 22 of 24 Swedish counties (except the city of Gothenburg and 10 surrounding municipalities) or between June 1, 1993, and June 30, 1994, in Malmöhus County, Sweden, were eligible for enrollment in the initial trial (Fig 1A).

Infants were vaccinated with a series of 3 intramuscular injections with

diphtheria-tetanus toxoids-pertussis/diphtheria-tetanus-acellular pertussis (DTaP) vaccines at ages 3, 5, and 12 months according to the Swedish vaccination schedule for diphtheria and tetanus toxoids at that time. In 2 counties, the trial diphtheria-tetanus toxoids-pertussis/DTaP vaccines were given at the age of 2, 4, and 6 months. Because different vaccines were compared in the initial study, infants enrolled in the study were vaccinated with a 2-, 3-, and 5-component acellular DTaP vaccine or a combined diphtheria, tetanus toxoids, wP vaccine. The 4 different vaccine groups were roughly the same size (Fig 1B).

The complete cohort was linked to the SMBR and the Swedish Prescribed Drug Register by using a personal identification number, a 10-digit identification code that all Swedish residents are assigned. Information was obtained from the SMBR concerning mother's country of birth, parity, maternal age at childbirth, maternal BMI, and smoking habits in early pregnancy, mode of delivery, maternal diseases and pregnancy complications, malformations, gestational age, and birth weight.

We excluded from the analyses data from 1331 individuals who were deceased at the time the register data were retrieved. The proportion of deceased was significantly higher among the nonvaccinated children during the vaccination period than among vaccinated children and children during the nonvaccination periods because the former group included chronically sick children who were contraindicated for the study. The overall death rates in the 4 different time periods, however, were fairly similar (Supplemental Table 4). We also excluded 4998 children with at least 1 malformation reported at birth. However, because minor malformations (undescended testicles, preauricular appendage, congenital nevus, and hip dislocation) were considered insignificant, children with

FIGURE 1

A, Timeline of study population with respect to time of birth, vaccination status and register data for asthma medication at 15 years of age. ^aThirty-four individuals were registered as vaccinated outside the vaccination period. ^bIn 2 counties, the trial vaccines were given at the age of 2, 4, and 6 months. B, Flowchart for study population: children born January 1, 1993, to December 31, 1994, in the study area (nonvaccinated versus vaccinated).

these conditions were included. Another 1042 individuals were excluded for various reasons, leaving a total of 199 665 individuals for the analyses (Fig 1B). The study was approved by the Regional Ethical Review Board, Faculty of Health Sciences at Linköping University.

Asthma Medication

Proxy indicators for asthma were based on data on dispensed prescriptions of asthma medication from the Swedish Prescribed Drug Register. This register is held by the Swedish National Board of Health and Welfare and contains data

with personal identification numbers about all prescribed and dispensed drugs for the entire Swedish population since July 1, 2005. Drug data are recorded according to their corresponding Anatomical Therapeutic Chemical code (Supplemental Table 5), not including drugs administered at hospitals.

The indicator “any asthma medication” was defined as at least 1 dispensed prescription of either a selective inhaled β_2 -agonist (R03AC), an inhaled corticosteroid (ICS; R03BA), a combination of an inhaled β_2 -agonist and

another drug for obstructive airway disease (R03AK04 through R03AK07), or a leukotriene antagonist (LTRA; R03DC03) over a period of 12 months commencing from the month of each child’s 15th birthday. Maternal asthma medication was linked to the corresponding child’s investigation period depending on which month and year the investigated subject was born (Fig 1A). A second indicator, labeled “anti-inflammatory treatment,” included ≥ 1 prescription of an ICS (including combinations of corticosteroids with other drugs; R03AK06 and R03AK07) and/or LTRAs during the same time period.

Other potential antiasthmatic drugs such as theophylline, oral corticosteroids, nedocromil, and cromolyn were not included in the analyses; these drugs are seldom used as standard treatment of asthma in Swedish teenagers.

Data Analysis and Confounders

Two main types of analyses were performed: an intention-to-treat analysis (ITT) and a per-protocol (PP) analysis. These were defined in a nonstringent manner and included some subjects not in the original study. In the PP analysis, vaccinated children registered in the initial trial were compared with nonvaccinated children born outside the vaccination period. In the ITT analysis, all children born in the vaccination period, whether they belonged to the immunized ($n = 79\,705$) or non-immunized ($n = 21\,485$) group, were compared with the nonvaccinated children born during the 5 months before and 7 months after the vaccination period. The influence of confounders was deemed to be different for these 2 types of analyses. To disentangle potential confounding in this study, a directed acyclic graph was used (Fig 2). This technique has been described before and is only outlined here.²² If an exposure and an outcome have a common ancestor (ie, a variable

with arrow paths directed to both of them), this situation may lead to confounding. In the directed acyclic graph, it is assumed that no causal relationships exist in the data other than those drawn as directed arrows into the graph. An arrow, however, does not imply that a causal relationship is present. Depending on what model we use in this study, we will have a different amount of confounders.

Instead of investigating only the association between vaccination and prescription (PP analysis), we initially studied the relationship between intended vaccination schedule and prescription. This setting allowed us to avoid certain types of confounders, described as Confounders 2 in Fig 2, and is referred to as “intent to treat” in the clinical trials setting. Treatment was allocated deterministically based on time of birth. Variables that might have changed during the 2-year period from which the cohort was collected might act as confounders. Controlling for time of birth per se was not possible because at every point in time, only one of the alternatives (offer vaccination/do not offer vaccination) was available. Instead, we had to try to control for the variables described as

Confounders 1 in Fig 2. The vaccination schedule was performed so that seasons were similar for vaccination and nonvaccination periods, enabling seasons to be omitted from several of the analyses. Variables that might have changed during the 2-year period from which the cohort was collected might act as confounders. Factors such as pollen counts and circulation of infections may have changed during the 2 years but could not be measured in this study. We tested whether time period was associated with the potential confounders. Spring 1993 (nonvaccination period) was compared with spring 1994 (vaccination period), and fall 1993 (vaccination period) with fall 1994 (nonvaccination period).

For the PP analysis, additional variables such as attitudes toward health care can act as confounders (Confounders 2 in Fig 2). We checked which of the potential confounders measured were associated with noncompliance in the vaccination period. For the ITT analysis, all confounders statistically associated with time period were included in the multivariate analysis. For the PP analysis, all statistically significant confounders for one or both of time period and compliance were used. Confounders

were added one at a time and all simultaneously for each scenario.

Pearson's χ^2 test was used to analyze categorical data on the univariate association between vaccination status and potential confounders and asthma medication. For continuous variables, a Wilcoxon test was used. A logistic regression model was used to calculate odds ratios (ORs) with 95% confidence intervals (95% CIs) as effect size for vaccination on asthma medication while controlling for numerous potential confounders. All analyses were performed by using R statistical software version 2.14.2 (R Foundation for Statistical Computing, Vienna, Austria).²³

RESULTS

The prevalence rates of dispensed anti-inflammatory medication or any asthma medication at the age of 15 years were 4.6% and 7.0%, respectively. In all, 7.3% of the girls and 6.6% of the boys had been dispensed any asthma medication at the age of 15 years. The corresponding numbers for antiinflammatory treatment were 4.5% and 4.7%, respectively. Table 1 presents vaccination and nonvaccination categories grouped according to gender, sociodemographic and perinatal indicators, and maternal asthma medication.

The ITT analysis found a slightly reduced risk of dispensed asthma medication in children born during the vaccination period, but the association disappeared after adjustment for confounding (Table 2). The type of vaccination schedule did not affect the association (data not shown). The PP analysis did not demonstrate any significant association between pertussis vaccination and dispensed asthma medication, and the vaccination schedule did not affect the association (data not shown).

Asthma medication was less likely to be dispensed in nonvaccinated children who were born during the vaccination period than in nonvaccinated children born outside the vaccination period.

FIGURE 2
Directed acyclic graph illustrating confounding in the study.

TABLE 1 Vaccinated and Nonvaccinated Infants During or Outside the Vaccination Period Grouped According to Gender, Sociodemographic, and Perinatal Indicators and Maternal Asthma Medication

Characteristic	Group A, % (n = 98 475)	Group B, % (n = 21 485)	Group C, % (n = 79 671)
Gender			
Female	48.9	49.4	49.1
Male	51.1	50.6	50.9
Gestational age, mo			
23–28	0.2	0.5	0.2
29–32	0.8	1.1	0.6
33–36	4.8	5.0	4.5
37–38	17.8	18.7	17.8
39–41	69.2	68.2	69.6
>41	7.1	6.4	7.2
Missing	0.1	0.2	0.1
Maternal age, y			
<20	2.3	2.8	2.2
20–24	19.8	20.5	19.4
25–29	38.7	37.6	39.5
30–34	26.7	26.1	26.6
35–39	10.5	11.0	10.5
≥40	2.0	2.1	1.9
Maternal smoking			
No	76.5	74.2	78.6
1–9 cigarettes/d	12.4	12.9	11.6
≥10 cigarettes/d	6.7	7.5	5.9
Missing	4.4	5.4	3.9
Cesarean delivery	11.5	11.1	11.3
Asphyxia (Apgar score <7)	0.8	1.1	0.6
Mother's country of birth			
Sweden	83.7	74.1	86.4
Missing	1.8	8.3	0.4
Mother's asthma medication	6.8	6.8	6.9

Group A, nonvaccinated, outside vaccination period; Group B, nonvaccinated, vaccination period; Group C, vaccinated, vaccination period. Data for 34 subjects were registered as vaccinated outside the vaccination period and are not displayed here.

The crude OR for dispensation of any asthma medication was 0.89 (95% CI: 0.84–0.94) and the corresponding OR for antiinflammatory treatment was 0.87 (95% CI: 0.81–0.94). These differences disappeared after adjustment for confounding (Table 3). Additional analyses conducted by using selective β_2 -agonists and ICS alone produced similar results (data not shown).

The type of pertussis vaccine did not affect the risk that asthma medication would be dispensed (Supplemental Table 6).

DISCUSSION

In this national cohort study, we investigated the potential impact of the pertussis vaccination of Swedish infants on dispensed asthma medication 15 years

later. The large study size should have enabled us to detect even minor effects. We found a weak negative association between vaccination and asthma medication in some of the analyses. When adjusting for several sociodemographic and perinatal factors, there was no difference in the prevalence of dispensed asthma medication between vaccinated and unvaccinated children in the cohort. Results of previous studies on the possible association of pertussis immunization and the development of asthma later in childhood have been contradictory.^{3,7,8,10,11,14,15} The first report about a possible increased risk of asthma in childhood after immunization against pertussis as an infant was published in 1994.³ The authors claimed that there was no other explanatory factor except pertussis vaccination, but it was difficult to assess the results because this rather short report lacked detailed information. Other studies reporting an increased asthma risk after infant immunization may have been significantly influenced by different kinds of bias such as the recall of potentially biased study variables on both exposure and outcome, as well as the problem of very small control groups^{7,10} or other types of bias rather than a biological effect.²⁴

Our findings are in line with a number of more recent studies that do not report any association between pertussis immunization and asthma.^{6,11,14,15} Methodologic difficulties were again noted in some of the studies, such as small control groups and low response rates,

TABLE 2 ORs, aORs, and 95% CIs for the Risk of Dispensed Asthma Medication at 15 y of Age

Treatment	Nonvaccinated OR	ITT Analysis		PP Analysis	
		Vaccination Period		Vaccinated	
		OR (95% CI)	aOR (95% CI) ^a	OR (95% CI)	aOR (95% CI) ^b
Any asthma medication	1	0.97 (0.93–1.00)	0.99 (0.95–1.03)	1.01 (0.97–1.04)	0.99 (0.95–1.03)
Antiinflammatory treatment	1	0.94 (0.90–0.98)	0.97 (0.92–1.01)	0.98 (0.94–1.02)	0.97 (0.92–1.01)

aOR, adjusted odds ratio.

^a Multivariate regression adjusted for maternal age, mother's country of birth, cesarean delivery, maternal smoking, asphyxia, mother's BMI, parity, and mother's asthma medication.

^b Multivariate regression adjusted for maternal age, mother's country of birth, gestational age, cesarean delivery, maternal smoking, asphyxia, mother's BMI, parity, mother's asthma medication, and child's respiratory distress.

TABLE 3 ORs, aORs, and 95% CIs for the Risk of Dispensed Asthma Medication at 15 y of Age According to Vaccination Status and Time Period

Treatment	Outside Vaccination Period		Vaccination Period			
	Nonvaccinated OR		Vaccinated		Nonvaccinated	
			OR (95% CI)	aOR (95% CI) ^a	OR (95% CI)	aOR (95% CI) ^a
Any asthma medication	1		0.99 (0.95–1.02)	0.99 (0.95–1.03)	0.89 (0.84–0.94)	0.99 (0.92–1.08)
Antiinflammatory treatment	1		0.96 (0.92–1.00)	0.96 (0.92–1.01)	0.87 (0.81–0.94)	0.99 (0.91–1.07)

^a Multivariate regression adjusted for maternal age, mother's country of birth, gestational age, cesarean delivery, maternal smoking, asphyxia, mother's BMI, parity, mother's asthma medication, and child's respiratory distress.

leading to the risk of biased results.^{6,11} The most recent study from the United Kingdom investigated a fairly large, representative population-based sample from which exposure and outcome measurements were collected prospectively and independently. The number of nonvaccinated children was again low, and parent-reported outcomes as well as vaccination status at the time of wheeze onset may have been misclassified.¹⁴

Certain studies even described a protective effect of immunization on the development of asthma and other allergic diseases but struggled with relatively small control groups of nonvaccinated children.^{12,13} Moreover, most of these studies used wP vaccines, which might induce a more prominent immunologic reaction than acellular vaccines, which typically exhibit lower reactogenicity regarding adverse events.²⁵ We found no differences in dispensed asthma medication, however, when comparing the 4 vaccines used in this trial, including 1 wP vaccine. To our knowledge, our study is the first to mainly investigate the effect of acellular pertussis vaccine on asthma medication on such a large scale. This claim is important because current pertussis vaccines mostly contain acellular pertussis vaccine, which has been reported to induce a more Th2/interleukin-dominated immune profile than wP vaccines; no increased risk of developing allergy was shown in a small sample, however.⁵

We were able to compare children vaccinated at 2, 4, and 6 months with chil-

dren vaccinated at 3, 5, and 12 months, and the timing of vaccination did not affect the outcome. In contrast, a previous study from Canada suggests that a vaccination delay of >2 months reduces the risk of asthma.²⁶ However, the Canadian study used retrospective data, which could have led to selection bias.

Because our study population contains almost an entire age group of the Swedish population with a 96% follow-up rate 15 years after infant immunization, we are confident that we present representative data. Information about exposure and outcome, vaccination status, and asthma medication was collected independently of each other and based on register information, minimizing the risk of any recall bias. Access to numerous potential confounding factors from the registries enabled us to further eliminate potential causes of asthma in this age group. To avoid certain types of confounding, such as parents' attitudes to vaccination and health care in general, we conducted an ITT analysis. Most previous studies were unable to account for this type of bias because control groups mainly included children whose parents decided not to vaccinate their children. This choice might have influenced the outcome of the studies because there is reason to believe that this group of individuals differs in more than just attitude to vaccination. This belief became obvious when we focused on the nonvaccinated children in our study. Dispensation of asthma medication was less likely among those born during the vaccination period than

among those born outside the vaccination period in the univariate analysis (Table 3). This difference disappeared after adjusting for multiple confounding factors.

Because misclassification of exposure may reduce the estimated effects in ITT analyses, we added a PP analysis. The true effect of vaccination on asthma medication could otherwise have been somewhat diluted. However, other factors might remain that may have changed during our study period and that we were unable to measure.

Because the nonvaccinated children born during the vaccination period form a heterogeneous group, the complete impact on our analysis cannot be easily clarified. It is known that it mainly includes children of parents who chose not to participate and who lived in larger urban areas in which participation rates had been lower than elsewhere. The fact that the dispensation of asthma medication was less likely among children in this group than among nonvaccinated children born outside the vaccination period, as seen in our unadjusted analysis, emphasizes the importance of the ITT analysis in this population. It underlines the assumption that parents' attitudes to vaccination and medication might influence the results.

Using asthma medication as a substitute for asthma disease or diagnosis has its limitations.²⁷ We focused, however, on dispensed ICS and LTRA because these drugs are prescribed mainly to individuals with active disease.²⁸ Moreover, we targeted an age group in whom the risk of treatment with

ICS and LTRA for issues other than asthma should be low.²⁹ We are confident that our outcome variable represents asthma disease and/or diagnosis, as a recent large Swedish validation study³⁰ found that asthma medication is a suitable proxy for asthma in children of this age. Because we did not investigate asthma medication in younger children, we cannot dismiss the possibility of an increased risk of transient asthma in the years immediately after immunization.

CONCLUSIONS

Immunization against pertussis in infancy has not entailed a higher risk of dispensed asthma medication at 15 years of age. These findings were independent of vaccine type and vaccine schedule. Our study presents evidence that pertussis immunization with common acellular vaccines in early childhood can be considered safe with respect to long-term development of asthma.

ACKNOWLEDGMENTS

The authors thank Professor Karin Fälth-Magnusson for critical remarks and for reviewing the manuscript. They also thank Dr Lennart Gustafsson who helped access the data from the former clinical trial and Mr Henrik Passmark, Swedish National Board of Health and Welfare, who helped link the different registers and build the database. The advice on language from Maurice Devenney is also gratefully acknowledged.

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www.pediatrics.org/cgi/doi/10.1542/peds.2014-0723

doi:10.1542/peds.2014-0723

Accepted for publication Jul 24, 2014

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: Dr Grünewald is currently employed at the Public Health Agency of Sweden in a project financed by Sanofi Pasteur MSD and GlaxoSmithKline. The other authors have indicated they have no potential conflicts of interest to disclose.

FUNDING: Dr Bråbäck was supported by the Umeå SIMSAM Node (Microdata research on childhood for lifelong health and welfare) financed by the Swedish Research Council. Drs Vogt and Nilsson were supported by The Swedish Asthma and Allergy Association (Stockholm, Sweden) and by ALF/LFoU grants, County Council of Östergötland. Financial support for the initial pertussis vaccine trial was obtained from the National Institute of Allergy and Infectious Diseases (N01-AI-15125). Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.