Adherence to the HPV Vaccine Dosing Intervals and Factors Associated With Completion of 3 Doses

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KEY WORDS

African Americans, contraception, immunization, insurance coverage, logistic models, medical specialty, medication adherence, papillomavirus infections, papillomavirus vaccines, patient compliance, pregnancy, uterine cervical neoplasms, vaccination

ABBREVIATIONS

HPV—human papillomavirus
HPV4—prophylactic human papillomavirus quadrivalent (types 6, 11, 16, and 18)
DMPA—depot medroxyprogesterone acetate
ACIP—Advisory Committee on Immunization Practices

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WHAT'S KNOWN ON THIS SUBJECT: Vaccination to prevent human papillomavirus infection is safe and effective. Rates of receiving all 3 doses after initiating vaccination range from 42% to 60%, according to early reports from managed health care organizations and the Centers for Disease Control and Prevention.

WHAT THIS STUDY ADDS: We determined that few female patients received the second and third human papillomavirus vaccine doses early, and most girls received the second and third doses either late or not at all. Race, health care use, and insurance were associated with completion.

abstract

OBJECTIVE: The objectives of this study were to determine (1) adherence to the immunization schedule for the human papillomavirus quadrivalent vaccine and (2) factors associated with completion of the 3-dose series.

METHODS: This was a retrospective review of health information records from an academic medical center. The sample included all 9- to 26-year-old female patients who initiated vaccination within 2 years after quadrivalent vaccine availability. Multivariable logistic regression models were estimated to determine associations with completion of the 3-dose series within 7 and 12 months.

RESULTS: Among the 3297 female patients who initiated vaccination with human papillomavirus quadrivalent vaccine, 67% self-identified as black and 29% self-identified as white. Fewer than 3% of vaccine doses were received earlier than recommended, but >50% of doses were received late. Completion rates were 14% by 7 months and 28% by 12 months. Independent predictors of completion by 7 months included white versus black race (odds ratio [OR]: 2.04 [95% confidence interval (CI): 1.64–2.56]; $P < .001$), use of contraception that required intramuscular injections every 3 months (OR: 1.53 [95% CI: 1.12–1.95]; $P < .001$), and private versus public insurance (OR: 1.31 [95% CI: 1.06–1.63]; $P < .05$). Age and clinic type were not independent predictors of completion.

CONCLUSIONS: Adherence to recommended intervals and completion of the vaccine series were low. Lower rates of completion in black patients compared with white patients raises concern that disparities in vaccine completion could exacerbate existing disparities in cervical cancer. *Pediatrics* 2011;127:77–84

Clinical trials have shown that the prophylactic human papillomavirus (HPV) quadrivalent (types 6, 11, 16, and 18 [HPV4]) vaccine is 94% to 100% effective in preventing anogenital precancers caused by types 16 and 18. More than 95% of women included in efficacy analyses received all 3 doses.[1–4] Complying with complete, timely vaccination for a 3-dose vaccine may pose difficulties for adolescents. Low vaccine-completion rates and/or prolonged intervals between doses may be a problem because, although robust immune titers are evident after the first and second dose of HPV4 vaccine,[5,6] the duration of protection and efficacy offered by incomplete immunization or immunization at intervals different from that of the clinical trials are currently unknown.

Evidence-based strategies to improve adolescent vaccine coverage rely mainly on studies of infant vaccination.[7,8] Understanding adherence to the HPV4 recommended vaccination schedule and identifying factors that predict completion among adolescents who initiate vaccination are necessary to develop evidence-based strategies to increase adherence among adolescents. Therefore, among those who received at least 1 HPV4 dose at a pediatric medical center, we sought to (1) describe the proportion of female patients who adhered to the recommended vaccination schedule and (2) determine factors associated with completion of the vaccine series.

POPULATION AND METHODS

This study was a retrospective health-information review approved by the institutional review boards at the authors' institutions.

Study Setting

The study setting is an independent, freestanding, full-service, not-for-profit, pediatric academic medical center that provides both primary and specialty care. Primary care is delivered by 2 divisions. The Division of General and Community Pediatrics delivers primary care to children and adolescents in 2 urban clinics. Almost 50 000 patient visits occur annually (85% Medicaid, 5%–10% private insurance, and 5%–10% self-pay). Seventy-five percent of patients self-report their race as black, and 25% as white. The Division of Adolescent Medicine delivers primary care at an urban, hospital-based clinic, hereafter referred to as "the base," to 11- to 22-year-olds, and provides gynecologic and adolescent medicine subspecialty care at the base and 9 suburban satellite clinics. In total, there are almost 23 000 patient encounters annually (45% Medicaid, 45% private insurance, and 10% self-pay); >80% occur at the base. Fifty-three percent of patients self-report their race as black, 42% as white, and 6% as other.

Source of Data

Records were obtained for female patients aged 9 to 26 years who received 1 or more HPV4 doses at Cincinnati Children's Hospital Medical Center from November 2006 (the time of the first dose given) to June 2008. Individuals were identified by searching the medical center data warehouse by using the Current Procedural Terminology code for HPV4 vaccine: 90649. Data were collected through June 2009 and included date of immunization, clinic administering the dose, payer; and patient's date of birth, self-reported race, history of depot medroxyprogesterone acetate (DMPA) use (diagnostic codes V25.02 and V25.49), and pregnancy-related visits (diagnostic codes V23.83, V22.2, V23.89, and V72.42B). Race was self-reported by the patient at the time of the clinical encounter.

Analytic Variables

Completion

We defined primary and secondary outcomes to examine completion of vaccination. The primary outcome, which represents Advisory Committee for Immunization Practices (ACIP) recommendations,[9] was defined as the patient receiving dose 3 within 213 days of dose 1 irrespective of the timing of dose 2. The secondary outcome, which represents recommendations from the HPV4 vaccine prescribing information,[10] was similarly defined and calculated using 365 days.

The Anderson-Aday Behavioral Model of Health-Services Use[11–14] provided the conceptual framework that guided choice of variables likely to predict completion of vaccination. Predictor variables included, at the time of HPV4 dose 1: the patient's age, race, and insurance coverage; whether the patient received DMPA; clinic location; time since vaccine availability (calculated as the number of days between the date of the first HPV4 vaccine given at Cincinnati Children's Hospital Medical Center and the date of dose 1); diagnosis of pregnancy; and use of DMPA during the patient's vaccine-completion period.

Vaccination Schedule

Adherence to the recommended vaccination schedule for each dose was defined a priori as the range of days between doses considered to be adherent. Lower limits were based on ACIP recommendations and expert opinion; upper limits were defined in consultation with clinicians and vaccine investigators.[9,10,15,16] During the study period, the following dosing intervals were recommended by the ACIP: 2 months between dose 1 and 2, with a minimum of 4 weeks; 6 months between dose 1 and 3, with a minimum of 24 weeks; and a minimum of 12 weeks between dose 2 and 3.[9,15] The

TABLE 1 Adherence to Recommended Dosing Intervals Among Female Patients Who Received at Least 2 HPV4 Doses

Dosing Interval	Definition of Adherence, d	No. (%) of Subjects		
		Nonadherent, Early	Adherent	Nonadherent, Late
Doses 1–2[a]	24–84	0 (0.0)	939 (40)	1427 (60)
Doses 2–3[b]	80–152	25 (1.8)	651 (46)	741 (52)
Doses 1–3[b]	164–213	33 (2.3)	438 (31)	949 (67)

[a] Among female patients who received at least 2 doses ($N = 2366$).
[b] Among female patients who received 3 doses ($N = 1477$).

minimum of 4 weeks was defined as 24 days.[16] For other intervals <4 months, the number of days in a month was defined as 28. For intervals 4 months or longer, the number of days in a month was defined as 30.5. Ranges of days are inclusive and stated in Table 1. Adherence to all 3 intervals was defined as receiving (*a*) dose 2 on time relative to dose 1, (*b*) dose 3 on time relative to dose 2, and (*c*) dose 3 on time relative to dose 1.

Statistical Analyses

During the study period, 69% of all HPV4 doses were delivered in the adolescent base clinic. Each adolescent satellite clinic delivered <1% of all doses, which is representative of the division's clinical practice (ie, a small proportion of visits occur at satellite clinics and the majority of these are for consultation; patients seen at satellite clinics generally receive vaccinations from their primary care provider). The 2 pediatric clinics delivered 14% and 10% of all doses. Specialty clinics other than Adolescent Medicine delivered 2% of all doses; the specific specialty was unidentifiable. Because of similarities in patient populations and health care settings at specialty sites, as well as the relatively small numbers of patients vaccinated at individual sites, the adolescent satellite clinics, other specialty clinics, and the 2 pediatric clinics were combined for analysis.

We examined associations between predictor variables and completion of vaccination within 7 and 12 months. χ^2 tests or Fisher's exact tests were used for categorical predictor variables and *t* tests for continuous predictor variables. The same subjects were included in these analyses. Age was analyzed as a continuous variable, dichotomous variable (9–18 and 19–26 years of age), and categorical variable.[15] Time since vaccine availability was analyzed as a continuous variable and as a categorical variable divided into 4 equal periods. We estimated logistic regression models including predictor variables that were significant at a *P* value of <.1 in bivariate analyses to estimate whether these factors were associated independently with outcome variables. We did not include pregnancy as a predictor in multivariable models because HPV4 vaccine is not recommended during pregnancy. Thus, very few patients with a diagnosis of pregnancy would have completed vaccination by 7 months, which would obscure relationships of interest in multivariable models.[17,18] Candidate predictors were subject to backward elimination until all remaining predictors had $P \leq .05$, adjusted for the other predictors remaining in the model. This procedure was applied separately to both the primary and secondary outcome variables. All reported *P* values are 2-tailed, and the study α value (.05) was 2-tailed and unadjusted for multiple tests.

TABLE 2 Characteristics of Female Patients Who Received Their First HPV4 Dose Between June 2006 and June 2008 ($N = 3297$)

Characteristic	Value
Age, mean (SD), y	15.3 (2.5)
Age group, *n* (%)	
9–10 y	140 (4.2)
11–12 y	515 (15.6)
13–18 y	2458 (74.6)
19–26 y	184 (5.6)
Race, *n* (%)	
Black	2218 (67.3)
White	942 (28.6)
Other[a]	137 (4.2)
Insurance used for HPV4 dose 1, *n* (%)	
Private	1007 (31.0)
Public	2144 (66.1)
None	94 (2.9)
Pregnancy during 12-mo completion period (yes), *n* (%)	66 (2.0)
DMPA at HPV4 dose 1 (yes), *n* (%)	346 (10.5)
DMPA during 7-mo completion period (yes), *n* (%)	647 (19.6)
DMPA during 12-mo completion period (yes), *n* (%)	728 (22.1)
Clinic location of HPV4 dose 1, *n* (%)	
Pediatrics	858 (26.0)
Adolescent base	2250 (68.2)
Adolescent satellite clinics	148 (4.5)
Specialty clinics	41 (1.2)
Time period of vaccine series initiation, *n* (%)	
November 2006—March 2007	478 (14.5)
April 2007—August 2007	1096 (33.2)
September 2007—January 2008	941 (28.5)
February 2008—June 2008	782 (23.7)

The denominator for percentages is the number of female patients who received at least 1 HPV4 dose. DMPA indicates depot medroxyprogesterone acetate.
[a] Includes Asian, mixed race, American Indian, and other.

RESULTS

The distributions of characteristics for all subjects are shown in Table 2. Most participants' race (96%) was black or white, and two-thirds used public insurance. Women older than 18 years were more likely to have private insurance than those 18 and younger (80% vs 28%; $P \leq .001$).

A total of 3297 female patients aged 9 through 26 years received at least 1 dose of HPV4 vaccine between November 2006 and June 2008. Among all subjects, 939 (28.5%) were adherent to the interval between dose 1 and 2, 651 (19.7%) were adherent to the interval

between dose 2 and 3, and 438 (13.3%) were adherent to the interval between dose 1 and 3. Only 378 female patients (11.5%) were adherent to all 3 intervals. Table 1 shows the proportion of subjects who received enough doses to complete the interval who were adherent, early, or late for each interval. The average time between dose 1 and 2 was ~6 months (188 days [SD: 161]) compared with the recommended 2 months. The average time between dose 1 and 3 was 11 months (330 days [SD: 157]) compared with the recommended 6 months.

The rates of completion at 7 and 12 months and associations with the predictor variables are shown in Table 3. In bivariate analyses, age, race, insurance, whether the patient received DMPA during the vaccine-completion period, and time since vaccine availability were associated with completion within both 7 and 12 months. Highest rates of completion occurred in patients who reported white race, used private insurance, used DMPA during the respective completion period, and initiated vaccination earliest in the study period.

Multivariable logistic regression models adjusted for all variables were estimated as described in "Population and Methods." Initial models showed that age and clinic location were not independently associated with completion of the vaccination series by 7 or 12 months, so subsequent models did not include these variables (Table 4). Patients who received DMPA within 7 months of the first HPV4 dose, compared with those who did not, had 1.5 times the odds of completing the HPV4 vaccine series within 7 months. Patients who received DMPA within 12 months of the first HPV4 dose, compared with those who did not, had 2.6 times the odds of completing the HPV4 vaccine series within 12 months. Patients who used private insurance,

TABLE 3 Rate of Completion of the 3-Dose HPV4 Vaccine Series Within 7 and 12 Months of Initiation of Vaccination ($N = 3297$)

Characteristic	7 mo		12 mo	
	n (%)	*P*[a]	*n* (%)	*P*[a]
Total	471 (14.3)	—	914 (27.7)	—
Age group, y				
9–10	18 (12.9)	.01	30 (21.4)	<.001
11–12	55 (10.7)	—	101 (19.6)	—
13–18	361 (14.7)	—	727 (29.6)	—
19–26	37 (20.1)	—	56 (30.4)	—
Race				
Black	246 (11.1)	<.001	528 (23.8)	<.001
White	204 (21.7)	—	349 (37.0)	—
Other[b]	21 (15.3)	—	37 (27.0)	—
Insurance used at HPV4 dose 1				
Private	190 (18.9)	<.001	327 (32.5)	<.001
Public	269 (12.5)	—	564 (26.3)	—
None	8 (8.5)	—	14 (14.9)	—
Pregnancy diagnosis				
Yes	2 (4.9)	.1	5 (7.6)	<.001
DMPA at HPV4 dose 1				
Yes	45 (13.0)	.47	104 (30.1)	.3
DMPA any time				
Yes	113 (17.5)	.009	274 (37.6)	<.001
Clinic location of HPV4 dose 1				
Pediatrics	101 (11.8)	.015	197 (23.0)	.002
Adolescent base	334 (14.8)	—	663 (29.5)	—
Adolescent satellite	31 (20.9)	—	46 (31.1)	—
Specialty clinics	5 (12.2)	—	8 (19.5)	—
Time period of vaccine series initiation				
November 2006—March 2007	85 (17.8)	<.001	162 (33.9)	.003
April 2007—August 2007	169 (15.4)	—	313 (28.6)	—
September 2007—January 2008	138 (14.7)	—	243 (25.8)	—
February 2008—June 2008	79 (10.1)	—	196 (25.1)	—

The denominators used to calculate percentages are the number of female patients with the reported characteristic. DMPA indicates depot medroxyprogesterone acetate.

[a] Derived from a χ^2 test, with the exception of pregnancy, for which a Fisher's exact test was used.

[b] Includes Asian, mixed race, American Indian, and other.

TABLE 4 Predictors of Completion of the HPV4 Vaccination Series Within 7 and 12 Months: Results of Multivariable Logistic Regression

	Vaccine-Completion Period			
	7 mo		12 mo	
	Adjusted OR	95% CI	Adjusted OR	95% CI
Race				
White vs black	2.04	1.64–2.56[a]	1.92	1.59–2.27[a]
White vs other[b]	1.35	0.83–2.22	1.45	0.96–2.22
Insurance				
Private vs public	1.31	1.06–1.63[c]	1.16	0.97–1.38
Public vs none	1.47	0.69–3.13	2.08	1.16–3.70[c]
DMPA any time[d]	1.53	1.21–1.95[a]	2.06	1.72–2.47[a]
Time since vaccine available, mo[e]	0.96[f]	0.94–0.98[a]	0.98[f]	0.96–0.99[g]

OR indicates odds ratio; CI, confidence interval; DMPA, depot medroxyprogesterone acetate.

[a] $P < .001$.

[b] Includes Asian, mixed race, American Indian, and other.

[c] $P < .05$.

[d] Receipt of depot medroxyprogesterone acetate at any time during the vaccine-completion period.

[e] Months since November 2006.

[f] Odds reported for each 1-month period since first dose given at Cincinnati Children's Hospital Medical Center.

[g] $P < .01$.

compared with those using public insurance, had 1.3 times the odds of completing the HPV4 vaccine series within 7 months. Patients who used public insurance, compared with those who used no insurance, had 2 times the odds of completing the HPV4 vaccine series within 12 months. White race compared with black race was independently associated with higher odds of vaccination completion within 7 months (odds ratio: 2.0) and 12 months (odds ratio: 1.9). In additional models, we examined the effects of age. In each model, the same variables were associated with outcomes.

DISCUSSION

In this study, we examined the rate of completion of the 3-dose HPV4 vaccine series and adherence to the recommended intervals between doses among female patients who initiated the vaccine series in academic clinical settings. We also examined factors associated with successful completion of the vaccine series.

In this population, we found a completion rate among those who initiated vaccination of 14.3% by 7 months. This is similar to the 13% completion rate by 6 months reported among those who initiated vaccination in a longitudinal study of women 13 to 26 years old recruited from the same adolescent base clinic shortly after HPV4 licensure.[19] However, our finding of a completion rate of 27.7% by 12 months is substantially lower than previously reported HPV4 vaccine-completion rates. In a managed health care organization, there was a 42.8% completion rate within 12 months among 9- to 26-year-old women who received their first HPV4 dose between October 2006 and March 2007.[20]

The rate of HPV4 vaccine series completion in our population was also lower than most reports of completion rates among those who initiated vaccination for other adolescent vaccines. Reported completion rates for the 3-dose hepatitis B vaccine have ranged from 11% to 73% in health maintenance organizations[21–23] and from 72% to 87% in academic health centers using reminder-recall and patient incentives for vaccination.[24,25] Examining more than half a million patient records from 7 managed-care organizations participating in the Vaccine Safety Datalink project between 1997 and 2004, Nelson et al[23] found that rates of hepatitis B vaccine completion within 1 year of the first dose among adolescents aged 9 to 12 years and 13 to 17 years were 63.4% and 45.1%, respectively. Completion rates of the 2-dose hepatitis A vaccine in the same age groups were 48.4% and 40.3%, respectively. Completion of the 2-dose varicella vaccine was 35.9% among 13- to 17-year-olds. Additional research is needed to understand reasons for nonadherence to adolescent vaccination recommendations and to test interventions to improve adherence.

Few women in our population received doses at intervals earlier than recommended, but most received the second and third doses at intervals that were substantially longer than recommended. Despite a provisional change in recommended intervals (dose 2 to be given 1–2 months after dose 1) in late 2009[26] that occurred after the completion of our analyses, our definitions of adherence were not compromised. Therefore, our reported rates reflect adherence to the current and previous recommendations.

In comparison to HPV4 clinical trials, mean completion rates in this population were lower and mean intervals between doses were longer (mean time between first and second dose was 6 months and between first and third dose was 11 months). Clinical improvement efforts should focus on timing of the second dose as well as completion of 3 doses. Little is known about the impact of incomplete vaccination and prolonged intervals on the immunogenicity and efficacy of HPV4 vaccine. Studies of hepatitis B vaccination reveal that a longer interval between doses 1 and 2 is associated with decreased antibody response.[27,28] However, longer intervals between doses 2 and 3 have been associated with increased antibody response.[27,29,30] This raises the concern, especially when dose 2 is delayed, that female patients may have lower immune responses than expected from published clinical trials. Lower immune responses could adversely impact vaccine efficacy or the duration of protection. Studies to examine immunogenicity at various dosing intervals are ongoing. However, given the robust immune response to each HPV4 dose and the importance of having immune protection before exposure to HPV, there is no current evidence to support withholding or delaying initiation of the HPV4 vaccine even if the clinician or patient is concerned that subsequent doses may be late. Current recommendations are to give dose 2 and 3 with no need to restart the series even if doses are substantially late.[9,26]

Identification of variables associated with adherence to immunization schedules in adolescents may help to explain reasons underlying poor adherence. Although 11- to 12-year-olds had the lowest rate of completion in unadjusted analyses, differences in completion rates according to age were not statistically significant in multivariable models. In addition, despite the fact that 19- to 26-year-olds were not eligible for the Vaccines for Children program, completion was higher in this age group compared with 9- to 18-year-olds in unadjusted analyses. The majority of older female patients used private insurance. Both public and private insurance coverage

were independently associated with completion, implying that insurance coverage is a key driver of vaccination completion.

An increased rate of completion was seen among patients who received DMPA. DMPA is an injectable form of birth control requiring clinic visits every 3 months, presumably increasing opportunities for vaccine delivery. Also, many women who use DMPA are or intend to be sexually active; thus, these women and/or their clinicians may perceive more need for vaccination against an infection transmitted through sexual contact. In addition, these women may be more accepting of intramuscular injections. This finding supports evidence showing the importance of decreasing missed opportunities for vaccination.[7] Because adolescents have a relatively low number of visits for preventive health care compared with visits for nonpreventive health care and visits to subspecialists,[31,32] the importance of decreasing missed opportunities for vaccination, including extending immunization programs beyond the medical home, is magnified.[33–35] Within our organization, these findings have strengthened efforts to improve established practices and introduce interventions to increase immunization rates.[7]

Female patients who self-identified as black, compared with those who self-identified as white, were less likely to complete vaccination within 7 and 12 months. This is consistent with previous reports of HPV4 vaccine completion[8,20,36,37] as well as hepatitis B vaccine completion in adolescents.[25,30,38] This disparity is concerning given that the incidence of and mortality from cervical cancer is higher among black women than white women in our community and nationally.[39–41] The reasons underlying racial disparities in completion are unclear, but beliefs and attitudes may play a role[42] as may access to health care. Findings from studies in which knowledge, beliefs, and attitudes about initiation of HPV vaccination are examined reveal that differences according to race exist.[43,44] Factors associated with initiating versus completing immunization may differ[19,45]: in future studies, factors that underlie the association between race and completion of the HVP4 series should be examined. Regardless, the health care community must be vigilant in providing education and access to all patients.

Clinic location was not associated with completion when controlling for patient-related factors. In the unadjusted analysis, differences in completion between clinic locations, including differences between the adolescent and pediatric clinics, were most likely caused by variations in the patient populations served, clinic policies, and clinician practice patterns that were immeasurable with accessible data sources. Given the limitations of the available data, we were unable to reliably measure additional factors that may influence completion, such as patient refusal of vaccination, for reasons such as adverse events after previous doses; other patient visits during the study period; and patient, parent, or provider vaccination attitudes and beliefs. In future studies, immunization status for HPV and other adolescent vaccines should be compared. Given this study involved only 1 medical center, and the participants were predominantly black, the findings may not be generalizable to other populations.

Limitations of the data set prevented reliable calculation of rate of initiation among all female patients who seek care at Cincinnati Children's Hospital Medical Center. To optimize HPV4 vaccine coverage, researchers who conduct future studies should aim to understand rates of and reasons for not initiating vaccination. After the study period ended, HPV4 vaccine received a permissive recommendation for use in male patients. It will be important to assess factors related to HPV4 vaccine adherence in male patients as they could differ from female patients. In addition, it is possible that subjects in this study received HPV4 doses at clinics outside of our medical center. Overall, this was unlikely to have had a large impact on our results because the pediatric and adolescent clinics in this study are the largest Medicaid providers in the area and have stable patient populations.

CONCLUSIONS

Among female patients who initiated vaccination within a freestanding pediatric academic medical center, white race and use of DMPA were associated with completion of vaccination. A concern raised by these findings is that racial disparities in cervical cancer rates in the United States may be exacerbated if noncompletion of the vaccine series or prolonged intervals between doses is associated with lower vaccine efficacy.

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MOLECULAR ANIMATION: *I suspect all of us remember some fairly dry lectures during medical school in which the function of different cellular molecules was described. I am old enough to remember a blackboard and 2x2 Kodachromes filled with static images. I could never quite understand how molecules got from here to there and how they interacted. Technology advances, however, may make cellular biochemistry as vivid, action packed, and easy to understand and remember as a Hollywood movie. As reported on* NewYorkTimes.com *(November 15, 2010:1–4), molecular animation is a burgeoning field. Molecular animators are scientists who understand cellular mechanisms and can also make use of the computer-based tools used to make feature films. The best animators begin with the science rather than the animation. Animators begin with freely available databases that contain three-dimensional coordinates for all of the atoms in a protein. Once the object can be represented, digital tools can make the object come alive with movement and change. The goal of the animation may be to better understand processes or to make others better understand the function of the molecule. While every attempt is made to base the animations on scientific underpinnings, by necessity, the animators have to speculate about certain effects. For example, all animations include color but in theory, the molecules depicted in most animations are too small to have any color. Some animations have been so lively and interesting that they have reached a much broader audience than the scientific community.* The Inner Life of the Cell *released in 2006 can be seen on YouTube and still generates thousands of hits. If a picture is worth a thousand words, how much is a video worth? I am hoping the next time I give a lecture, I'll find out.*

Noted by WVR, MD