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Immunogenicity of quadrivalent human papillomavirus vaccine among Alaska Native children aged 9–14 years at 5 years after vaccination

Bionca M. Davis[a,b], **Ian Blake**[a], **Gitika Panicker**[c], **Elissa Meites**[d], **Gail Thompson**[a], **Jesse Geis**[a], **Dana Bruden**[a], **Marc Fischer**[a,*], **Rosalyn Singleton**[a,e], **Elizabeth R. Unger**[c], **Lauri E. Markowitz**[d], **Michael G. Bruce**[a]

[a]Arctic Investigations Program, Division of Infectious Disease Readiness and Innovation, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Anchorage, AK, USA

[b]Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, Georgia

[c]Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

[d]Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

[e]Alaska Native Tribal Health Consortium, Anchorage, AK, USA

Abstract

Background: Persistent human papillomavirus (HPV) infection can cause anogenital and oropharyngeal cancers. Many HPV infections and HPV-associated cancers are vaccine-preventable. Studies suggest long-term persistence of vaccine-induced antibodies. However, data are limited among Alaska Native people.

Methods: During 2011–2014, we enrolled Alaska Native children aged 9–14 years who received a 3-dose series of quadrivalent HPV vaccine (4vHPV). We collected sera at 1 month and 1, 2,

*Corresponding author at: Arctic Investigations Program, Division of Infectious Disease Readiness and Innovation, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Anchorage, AK, USA. mfischer@cdc.gov (M. Fischer).

CRediT authorship contribution statement

Bionca M. Davis: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Ian Blake:** Data curation, Formal analysis, Methodology, Writing – review & editing, Visualization. **Gitika Panicker:** Formal analysis, Investigation, Writing – review & editing. **Elissa Meites:** Conceptualization, Methodology, Writing – review & editing. **Gail Thompson:** Data curation, Investigation, Project administration. **Jesse Geis:** Data curation, Project administration. **Dana Bruden:** Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Marc Fischer:** Data curation, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Rosalyn Singleton:** Conceptualization, Methodology, Writing – review & editing. **Elizabeth R. Unger:** Conceptualization, Formal analysis, Supervision, Writing – review & editing. **Lauri E. Markowitz:** Conceptualization, Project administration, Supervision, Writing – review & editing. **Michael G. Bruce:** Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

3, and 5 years post-vaccination to evaluate trends in type-specific immunoglobulin G antibody concentrations for the 4vHPV types (HPV 6/11/16/18).

Results: All participants (N = 469) had detectable antibodies against all 4vHPV types at all timepoints post-vaccination. For all 4vHPV types, antibody levels peaked by 1 month post-vaccination and gradually declined in subsequent years. At 5 years post-vaccination, antibody levels were higher among children who received 4vHPV at a younger age.

Conclusions: Alaska Native children maintained antibodies against all 4vHPV types at 5 years post-vaccination.

Keywords

Human papillomavirus; Human papillomavirus recombinant vaccine; quadrivalent; Types 6, 11, 16, 18; Immunogenicity, Vaccine; Cohort studies; Alaska Natives; United States

1. Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States, causing more than 13 million new infections per year [1,2]. Most infections are asymptomatic and resolve within 1–2 years. However, persistent infection can lead to cancer. Each year in the United States, HPV causes an estimated 37,300 cases of cervical, other anogenital, or oropharyngeal cancer [3].

HPV infection and HPV-associated cancers are vaccine-preventable. Because HPV vaccination is most beneficial before the start of sexual activity, the Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of all children aged 11–12 years; vaccination can be given starting at age 9 years [4]. Quadrivalent HPV vaccine (4vHPV), which prevents new infections with HPV types 6, 11, 16, and 18, was introduced in the United States in 2006 and was the predominant HPV vaccine administered through 2015 [4]. Since 2016, 9-valent HPV vaccine (9vHPV) has been the only HPV vaccine available in the United States. HPV vaccines have been licensed and introduced in more than 117 countries and most vaccine used has been 4vHPV [5]. Evaluating the long-term antibody response to 4vHPV can inform future recommendations for people who completed the 4vHPV series.

Historically, Alaska Native women had high rates of cervical cancer compared to non-Hispanic White females in the United States [6]. Cervical cancer rates among Alaska Native women have since declined but disparities persist [6]. HPV vaccines are highly effective for preventing new HPV infections and studies suggest long-term persistence of vaccine-induced antibodies [7,8]. However, data are lacking on long-term response to HPV vaccine among Alaska Native children. We previously reported safety and immunogenicity data up to 2 years after the third dose of 4vHPV among Alaska Native children aged 9–14 years [9]. In this analysis, we evaluate the long-term immunogenicity among these same study participants up to 5 years post-vaccination and use modeling to predict antibody levels at 10 years after vaccination.

2. Methods

Study design and participants.

We conducted a prospective cohort study of children receiving a 3-dose series of 4vHPV [9]. Alaska Native children aged 9–14 years who were eligible for services at the Alaska Native Medical Center were enrolled between May 2011 and July 2014. This study was initially designed to include only girls based on the 2006 ACIP recommendations for routine vaccination of girls in the United States. ACIP recommendations were expanded in 2011, and we began to enroll boys in August 2013. Enrolled participants were asked to provide a serum specimen at 1 month, 1 year, 2 years, 3 years, and 5 years after receiving the third dose of vaccine. Prior to each study visit, research staff reviewed the state immunization registry and patient medical records for receipt of additional doses of an HPV vaccine. Participants who received additional doses of 4vHPV or 9vHPV were ineligible for further study visits.

The research protocol was approved by Alaska Area Institutional Review Board, the CDC Institutional Review Board, the Alaska Native Tribal Health Consortium, and the Southcentral Foundation. We obtained written informed assent from study participants and informed consent from their parents. Participants were given a gift card at each study visit.

Laboratory testing.

As previously described, we used a multiplex virus-like particle enzyme-linked immunosorbent assay to measure type-specific immunoglobulin G (IgG) antibody titers for the 4vHPV types 6, 11, 16, and 18 [10]. Cutoff values for defining seropositivity against each HPV type were established using anonymized sera from 50 children (sera provided by Dr. J. Dillner, Lund University, Sweden). For the purpose of this analysis, antibody positivity was defined as ≥0.1 arbitrary units [AU]/ml for anti-HPV-6 and anti-HPV-11, ≥0.5 international units [IU]/ml for anti-HPV-16, and ≥0.4 IU/ml for anti-HPV-18.

Statistical analysis.

We determined the proportion of participants with detectable antibodies at 5 years post-vaccination and calculated HPV type-specific antibody geometric mean concentrations (GMC) at each timepoint to evaluate trends over time. Results are reported for all participants with data at that timepoint and stratified by sex and age at the first dose. Study visit windows were based on time since the third dose and defined as follows: 1 to 275 days for month 1; 0.76–1.75 years for year 1; 1.75 to 2.75 years for year 2; 2.75 to 3.75 years for year 3; and 4.25 to 5.75 years for year 5. T tests were performed on log-transformed data to compare GMC by sex and age at vaccination. Linear regression was used to control for sex when comparing by age at vaccination. Analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 3.0 (https://www.r-project.org).

Piecewise linear mixed effects modeling on a logarithmic scale was used to examine the observed rates of decay and predict the future decay in immunogenicity among the four HPV types for patients with data at all timepoints. Each HPV type log-linear model was fitted on three consecutive time intervals, with break points at 7, 12, and 21 months based on

observed decay [11]. The respective models were used to construct estimates of the 10-year follow-up GMCs for each type. Models incorporated age at first dose, sex, and binned peak immune response as influences on decay. The model was fitted using the GLIMMIX procedure in SAS.

3. Results

Of 525 enrolled participants, 477 participants completed the 3-dose series and had at least one follow-up visit. Eight participants subsequently withdrew or received a dose of 9vHPV and were excluded from this analysis. Of the remaining 469 participants, 432 (92%) had antibody data available at 1 month after completing the 3-dose series, 381 (81%) at 1 year post-vaccination, 359 (77%) at 2 years, 367 (78%) at 3 years, and 344 (73%) at 5 years. Overall, 199 (42%) participants had data available at all five timepoints post-vaccination.

Most of the 469 study participants were female (n = 398, 85%) (Table 1). The median age at enrollment was 11 years (range, 9–14 years). All participants had detectable antibodies against the 4vHPV types at all timepoints post-vaccination. Antibody levels peaked by 1 month post-vaccination, declined substantially during the next year, and gradually declined in subsequent years (Fig. 1). GMC at 5 years post-vaccination were significantly lower than those at 1 month, 1 year, and 2 years after the third dose of vaccine but not significantly lower than those at 3 years post-vaccination. For anti-HPV-16, GMC declined from 1,237 IU/ml (95% CI 1,123–1,362) at 1 month post-vaccination to 230 IU/mL (95% CI 204–259) at 1 year, 171 IU/mL (95% CI 153–192) at 2 years, 137 IU/mL (95% CI 121–154) at 3 years, and 110 IU/mL (95% CI 98–124) at 5 years (Table 2). Trends in antibody levels from 1 month to 5 years post-vaccination were similar for the other three 4vHPV types.

At 5 years post-vaccination, GMC decreased with increasing age at first dose of 4vHPV (Fig. 2). For example, for anti-HPV-16 the 5-year GMC for those who received their first dose at 9 years of age was 143 IU/ml (95% CI 141–144) compared to 39 IU/ml (95% CI 37–42) among those vaccinated at 14 years of age. Findings were similar for other types. GMC were higher among females than males for all 4vHPV types; however, these differences were not significant after adjusting for age.

The log-linear piecewise model predicted durable long-term immunogenicity to all 4vHPV types. Based on the current rate of decline, the predicted GMC at 10 years post-vaccination was 9 AU/mL (95% CI 7–13) for anti-HPV-6, 12 AU/mL (95% CI 9–16) for anti-HPV-11, 47 IU/mL (95% CI 35–52) for anti-HPV-16, and 14 IU/mL (95% CI 10–19) for anti-HPV-18.

4. Discussion

In this longitudinal study among Alaska Native children who received 4vHPV at age 9–14 years, all participants still had detectable antibodies against all 4vHPV types at 5 years post-vaccination. Anti-HPV antibody GMC were highest at 1 month after completing the 3-dose regimen, declined during subsequent years, and persisted for at least 5 years. At 5 years post-vaccination, antibody levels were higher among children who received 4vHPV

at a younger age. These findings are consistent with other long-term HPV immunogenicity studies conducted among children and adults [6,7,12,13].

Similar to a previous study that followed participants up to 10 years post-vaccination, we found that antibody levels at 5 years after vaccination were inversely associated with age at first vaccination [6]. Previously published findings from our study showed that at 1 month after the third dose of 4vHPV, GMC were higher among children who initiated vaccination at age <11 years [9]. Taken together, these findings further support recommendations that HPV vaccine can be given starting at age 9 years [4]. In our study, GMC were higher among females than males at all time points; however, female participants also were younger. Similar to the previously published results from this and other studies, after adjusting for age at initial vaccination, we did not observe significant differences between the GMC of males and females at years 3 and 5 post-vaccination [6,9]. In contrast, a metanalysis of 18 studies that evaluated sex-based differences in antibody response to 4vHPV found that females tended to have higher GMC than males but these differences were only statistically significantly for anti-HPV-6 [14].

Using a piecewise linear model and observed rates of decay from this study through 5 years after vaccination, we estimate that antibody GMC will remain above the threshold of detection for all 4vHPV types at 10 years post-vaccination. Based on a prior study, the rate of decay is expected to decrease between the 5 year and 10 year follow up visits [11]. If that finding holds, our model provides a conservative estimate and GMC at 10 years may be higher than we predicted.

Our study has several limitations. We may be underpowered to detect sex-based differences due to the small sample size among male children. This study evaluates 4vHPV, which is no longer used in the United States; we expect the antibody response against HPV types 6, 11, 16, and 18 to be similar following vaccination with 4vHPV and 9vHPV [15]. Similarly, we evaluated antibody levels following a 3-dose regimen of 4vHPV but expect a similar response and rates of decline following the currently recommended 2-dose regimen for children who receive their first HPV vaccination before age 15 years [16,17]. In addition, a pre-vaccination blood sample was not collected prior to vaccination so it is not known if any participants had pre-existing antibodies. Finally, there is no immunologic correlate of protection for HPV infection, so we cannot determine if the GMC observed at 5 years post-vaccination will protect against persistent HPV infection. However, HPV infection is rare in people who have received HPV vaccine and efficacy and effectiveness studies suggest long-term protection against infection and other outcomes [2,7,18–20].

This is the first long-term study of HPV vaccine immunogenicity among Alaska Native children and confirms that the antibody response is similar to that of children included in pre-licensure trials. At 5 years post-vaccination, all participants still had detectable antibodies against all 4vHPV types and antibody levels were higher among children who received 4vHPV at a younger age. These results support other long-term immunogenicity studies indicating an HPV vaccine booster dose is not needed and reinforces the recommendation that all children, including Alaska Native children, should continue to receive HPV vaccine according to CDC recommendations and that vaccine can be given

starting at age 9 years. We plan to continue to follow this cohort to evaluate the long-term antibody response up to 20 years post-vaccination.

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Disclaimer

The findings and conclusions in this article are those of the authors and do not necessarily represent the official positions of the Centers for Disease Control and Prevention.

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Data availability

The data that has been used is confidential.

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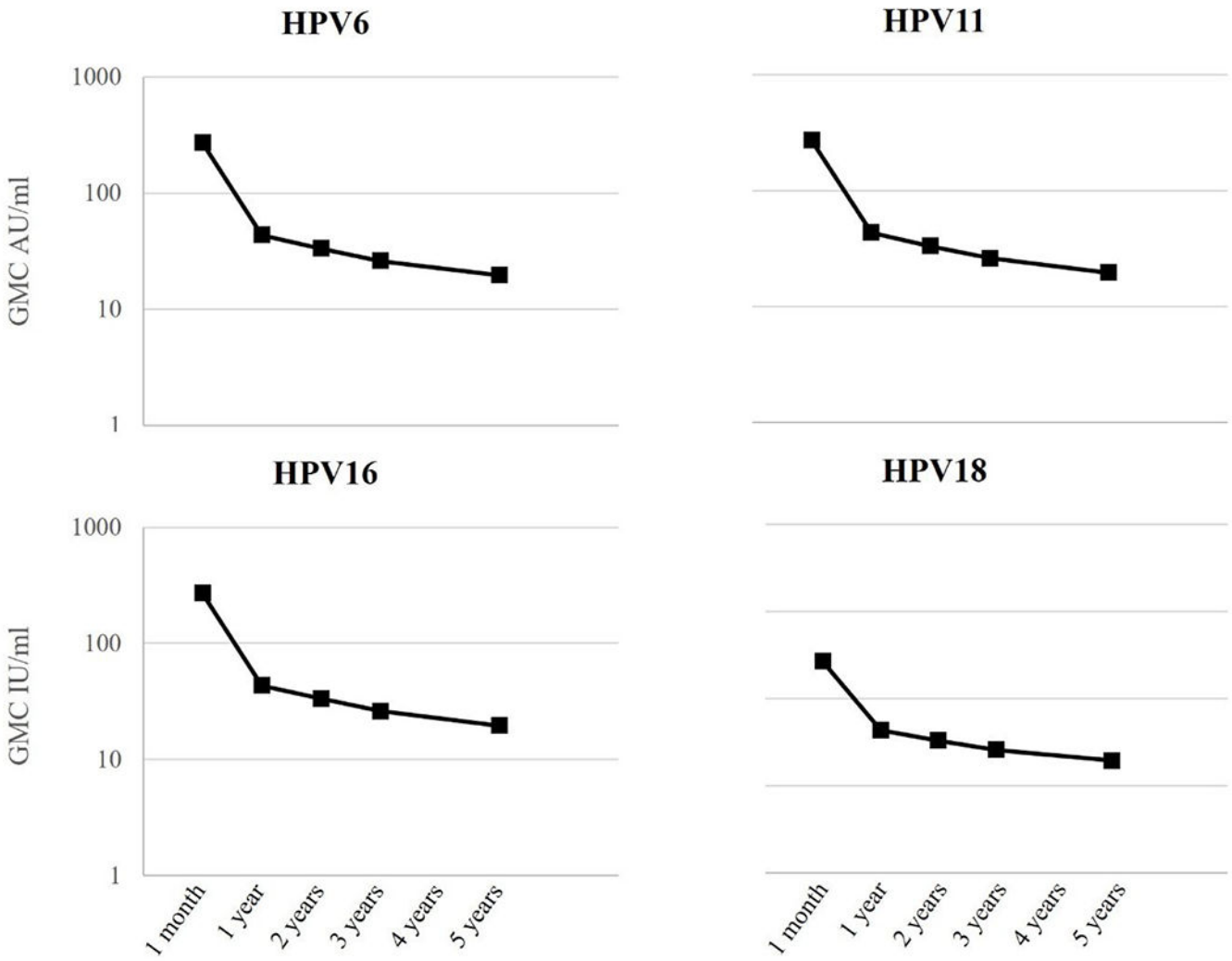

Fig. 1.

Geometric mean concentrations (GMC) for type-specific human papillomavirus (HPV) immunoglobulin G antibody among Alaska Native children who completed a 3-dose series of quadrivalent HPV vaccine, by time post-vaccination. Note: AU = Arbitrary Units, IU = International Units.

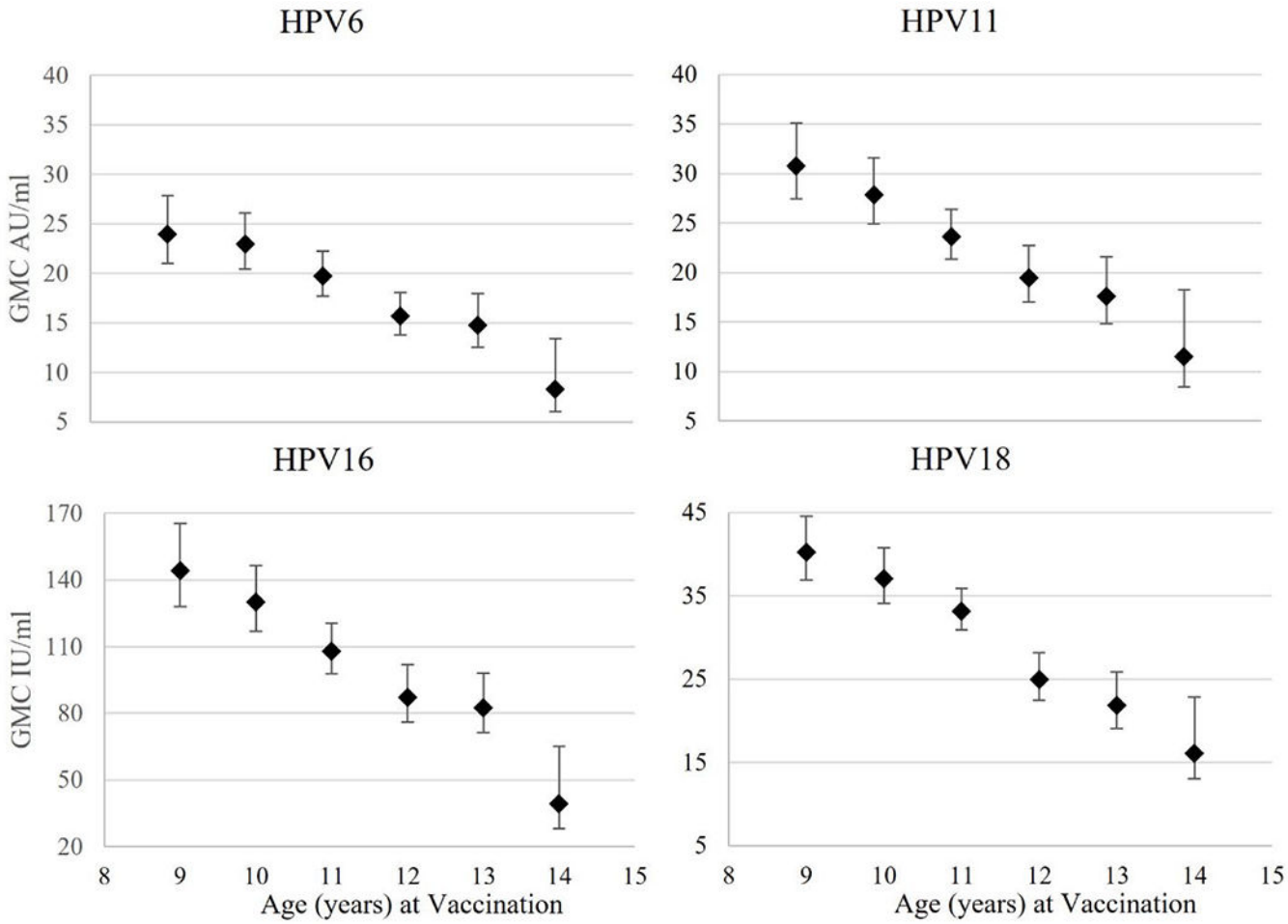

Fig. 2.

Geometric mean concentrations (GMC) and 95% confidence intervals for type-specific human papillomavirus (HPV) immunoglobulin G antibody among Alaska Native children at 5 years after completing a 3-dose series of quadrivalent HPV vaccine, by age at first dose.

Note: AU = Arbitrary Units, IU = International Units.

Table 1

Participant age at enrollment by sex for a cohort of Alaska Native children who completed a 3-dose series of quadrivalent human papillomavirus (4vHPV) vaccine and had at least one follow-up study visit.

	Female [N = 398]		Male [N = 71]	
Age at enrollment	**No.**	**(%)**	**No.**	**(%)**
9–10 years	196	(49)	22	(31)
11–12 years	164	(41)	28	(39)
13–14 years	38	(10)	21	(30)

Table 2

Geometric mean concentrations (GMC) and 95% confidence intervals for type-specific human papillomavirus (HPV) immunoglobulin G antibody among Alaska Native children who completed a 3-dose series of quadrivalent HPV vaccine, by time post-vaccination.

Time post-vaccination	No.	HPV6 [AU/mL]		HPV11 [AU/mL]		HPV16 [IU/mL]		HPV18 [IU/mL]	
1 month	432	269	(243–297)	348	(317–382)	1,237	(1,123–1,362)	491	(437–551)
1 year	381	43	(38–49)	56	(50–63)	230	(204–259)	73	(64–84)
2 years	359	33	(29–38)	43	(38–48)	171	(153–192)	53	(47–61)
3 years	367	26	(23–29)	34	(30–38)	137	(121–154)	40	(35–46)
5 years	344	20	(17–22)	24	(21–27)	110	(98–124)	32	(28–37)

Note: AU = Arbitrary units; IU = International units.