Differential Regulation of Interleukin (IL)–4, IL-5, and IL-10 during Measles in Zambian Children

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To determine the effect of measles virus infection on cytokine production in children from sub-Saharan Africa, temporal changes in cytokine production in vivo were analyzed and the T cell sources of type 1 and type 2 cytokines were identified in Zambian children with measles. The immune response during measles involved early type 1 responses, with production of interferon-γ by $CD8^+$ T cells and of interleukin (IL)–2 by $CD4^+$ T cells. Subsequently, more-prolonged increases were observed in the type 2 cytokines IL-4 and IL-13, both produced by $CD4^+$ T cells. IL-5 was regulated differently from IL-4 and IL-13: levels were low compared with levels in control children and were reflected in lower eosinophil counts during measles. Immunoglobulin E was lower in children with measles, despite high levels of IL-4 and IL-13. Plasma levels of IL-10 were elevated for weeks, potentially contributing to impaired cellular immunity and depressed hypersensitivity responses following measles.

Measles remains an important cause of child mortality, particularly in Africa and the Asian subcontinent [1], and most deaths are due to secondary infections resulting from the accompanying immunosuppression [2–4]. For several weeks after measles, delayed-type hypersensitivity skin test responses to recall antigens are depressed [4, 5], and there is an increased susceptibility to other infections and autoimmune encephalomyelitis [6]. In vitro, lymphoproliferative responses to mitogens are diminished [7, 8]. Despite these immunologic abnormalities, measles virus is cleared, and a long-term protective immune response is established.

An appropriate immune response to viral infection involves recognition of the pathogen by the innate immune system, expansion of antigen-specific T and B cells important for pathogen clearance, and subsequent termination of the inflammatory process. Activation and regulation of these immune responses requires complex interactions between many cell types and soluble factors. Cytokines play an important role in the development and control of the immune response and function as immune effectors and regulators. In mice, T cells can be subdivided into type 1 cells, which produce interleukin (IL)–2, interferon (IFN)–γ, and lymphotoxin, and type 2 cells, which produce IL-4, IL-5, and IL-13. This segregation correlates well with the effector functions of type 1 T cells in delayed-type hypersensitivity and cell-mediated immunity and of type 2 T cells in providing help to B cells for antibody production. Type 1 and type 2 cells are cross-regulatory, and murine models show that the type of immune response induced by infection is often an important determinant of susceptibility or resistance [9]. In humans, the array of cytokines produced and their effects are similar to those in mice, but the type 1/type 2 T cell paradigm is less clear.

Measles virus infects monocytes/macrophages, epithelial cells, and endothelial cells [10, 11], all potential cellular participants in the innate response and early sources of cytokines. Measles virus directly down-regulates monocyte and dendritic cell production of IL-12, an important cytokine for differentiation of type 1 T cells [12, 13]. Nevertheless, measles virus–specific $CD4^+$ and $CD8^+$ T cells with capacities for cytotoxicity, proliferation, and production of multiple cytokines are stimulated and expanded in lymphoid tissue, appear in the blood, and infiltrate sites of viral replication [14–17]. B cells are stimulated to produce IgM and maintain levels of high-titer, high-affinity measles virus–specific IgG. Characterization of the plasma cytokine profiles of US and Peruvian children with measles has shown that IFN-γ and IL-2 are produced during the rash [18], but the cellular sources of these type 1 cytokines are not known. As virus is cleared and the rash fades, IL-4 becomes elevated, suggesting a shift toward cytokines that provide B cell help important for

Received 15 March 2002; revised 23 May 2002; electronically published 13 September 2002.

Written informed consent was obtained from the parents or guardians of the children studied. The study protocol was reviewed and approved by the institutional review boards at Johns Hopkins University, Bloomberg School of Public Health, Baltimore, and the University Teaching Hospital, Lusaka, Zambia.

Financial support: National Institutes of Health (AI-23047); World Health Organization; Wyeth-Lederle Vaccines and Pediatrics Young Investigator Award in Vaccine Development of the Infectious Disease Society of America (to W.J.M.).

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The Journal of Infectious Diseases 2002; 186:879–87

0022-1899/2002/18607-0001$15.00

Table 1. Plasma levels of interferon (IFN)–γ and soluble interleukin-2 receptor (sIL-2R), in children with measles and in control children without measles..

Group, time point	IFN-γ				sIL-2R			
	No. of children	Mean, pg/mL (SD)	Median, pg/mL (IQR)	P^a	No. of children	Mean, U/mL (SD)	Median, U/mL (IQR)	P^a
⩽3 days after rash onset	25	127 (155)	76 (40–128)	.02	44	3885 (2143)	3569 (2453–4510)	.0001
4–7 days after rash onset	33	84 (199)	30 (10–48)	.2	53	3403 (1776)	3014 (2307–4163)	.0001
8–14 days after rash onset	7	37 (17)	26 (25–56)	.1	21	3175 (1324)	3118 (2451–3478)	.001
1–month follow-up	31	63 (84)	29 (21–55)	.1	38	1713 (822)	1378 (1151–2198)	.2
Control children	23	117 (170)	10 (10–266)		27	1987 (944)	1757 (1274–2274)	

NOTE. HIV, human immunodeficiency virus; IQR, interquartile range.
[a] Comparison with HIV-uninfected control children.

antibody production. One hypothesis for measles virus–induced immunosuppression is that IL-4, and perhaps other type 2 cytokines important for B cell maturation and differentiation, suppresses monocyte/macrophage responses to subsequent pathogens, resulting in the increased susceptibility to secondary infection after measles [19].

Immune responses to measles virus can be influenced by nutritional deficiencies and by ongoing immune responses to current and past infections, both likely to be problems in developing countries, where measles is most prevalent. To determine the effect of measles virus infection on cytokine production in children from sub-Saharan Africa and to expand our knowledge of the process of immunoregulation during measles, we analyzed the temporal changes in plasma cytokine levels and identified the T cell sources of representative type 1 and type 2 cytokines in Zambian children with measles.

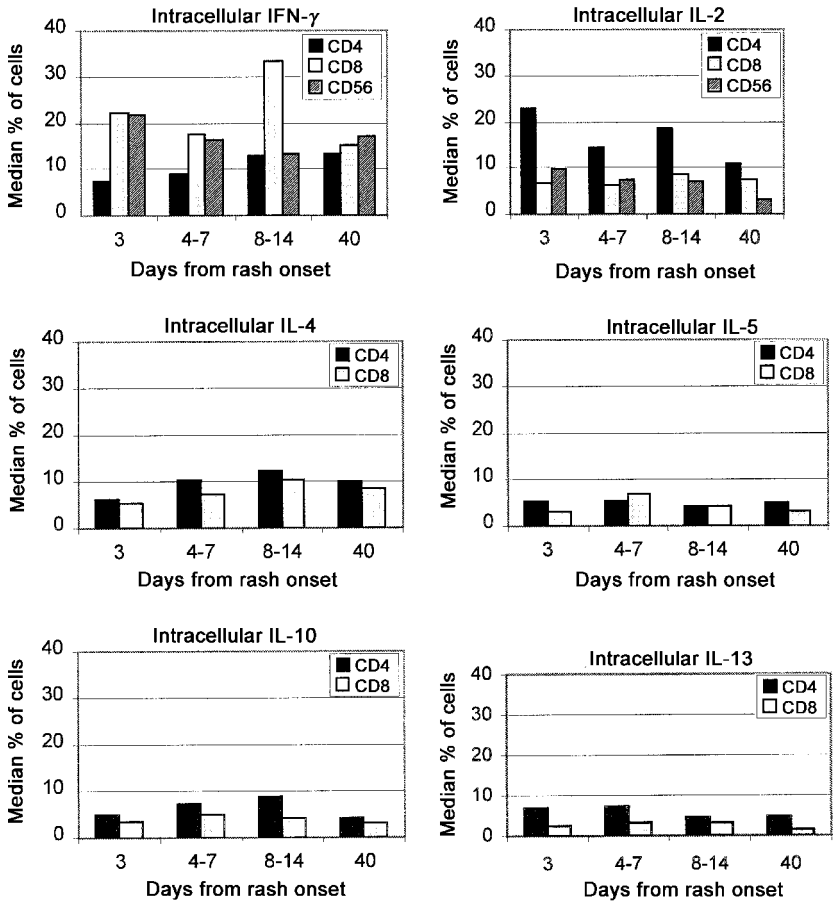

Figure 1. Intracellular cytokine staining of lymphocyte subsets in children with measles. IFN, interferon; IL, interleukin.

Table 2. Plasma levels of type 2 cytokines, IgE, and eotaxin, in children with measles and in control children without measles.

	IL-4				IL-13				IgE				Eotaxin			
Parameter, time point	No. of children	Mean, pg/mL (SD)	Median, pg/mL (IQR)	P^a	No. of children	Mean, pg/mL (SD)	Median, pg/mL (IQR)	P^a	No. of children	Mean, IU/mL (SD)	Median, IU/mL (IQR)	P^a	No. of children	Mean, pg/mL (SD)	Median, pg/mL (IQR)	P^a
≤3 days after rash onset	29	32 (41)	15 (15–31)	.06	42	65 (60)	42 (15–105)	.06	20	89 (170)	13 (5–126)	.1	32	22 (11)	20 (14–28)	.005
4–7 days after rash onset	35	115 (392)	15 (15–50)	.001	50	61 (51)	45 (15–85)	.02	35	56 (99)	11 (5–64)	.04	31	25 (18)	19 (15–35)	.003
8–14 days after rash onset	17	30 (37)	15 (15–36)	.09	18	54 (46)	40 (15–73)	.1	15	53 (87)	5 (5–54)	.08	10	17 (8)	15 (13–18)	.1
1-month follow-up	37	53 (94)	15 (15–48)	.002	51	54 (50)	42 (15–66)	.1	29	94 (226)	25 (5–50)	.1	24	20 (19)	15 (12–22)	.1
Control children	52	16 (7)	15 (15–15)		36	47 (56)	15 (15–56)		19	154 (226)	118 (5–226)	.1	17	16 (8)	12 (12–12)	

NOTE. HIV, human immunodeficiency virus; IL, interleukin; IQR, interquartile range.
[a] Comparison with HIV-uninfected control children.

Subjects and Methods

Subjects. We studied children hospitalized at the University Teaching Hospital, Lusaka, Zambia, between January 1998 and October 2000 who had a clinical diagnosis of measles (fever and maculopapular rash with conjunctivitis, rhinorrhea, or cough). Children who were severely ill or who died within hours of admission were less likely to be enrolled. In addition, the number of children enrolled per day was limited by the laboratory's capacity for processing specimens. Parents or guardians were asked to return with the child 1 month after discharge, but active tracing of children who failed to return was not done. A blood specimen and clinical information were collected at hospital admission, discharge, and a 1-month follow-up visit. Human immunodeficiency virus (HIV)–uninfected children with measles were compared with a group of HIV-uninfected children without acute illness, who were recruited from a well-child clinic or local school and confirmed to be negative for IgM antibody to measles virus.

Specimen collection and processing. Blood specimens were collected in EDTA tubes and transported to the laboratory. Aliquots of whole blood were removed for white blood cell counts and monoclonal antibody staining for flow cytometry. White blood cell counts and differential white blood cell counts were determined manually. Plasma was separated and stored in aliquots at −70°C for later measurement of plasma levels of antibodies to measles virus and HIV, HIV RNA, IgE, cytokines, and eotaxin.

Detection of measles virus IgM antibody. Measles was confirmed by detection of measles virus–specific IgM in plasma by EIA (Wampole Laboratories). Children were classified as having measles if measles virus–specific IgM was detected at any time point.

Detection of HIV RNA. Plasma was tested for antibody to HIV by EIA (Organon Technika). Plasma samples from children with a positive result of EIA for antibody to HIV were assayed for HIV RNA. Plasma levels of HIV RNA were quantified by a reverse-transcription polymerase chain reaction assay (Amplicor HIV-1 Monitor version 1.5; Roche Molecular Systems). Children were classified as being HIV infected if HIV RNA was detected in a plasma sample from any time point and were excluded from subsequent analysis.

Plasma cytokine, cytokine receptor, chemokine, and IgE levels. Plasma levels of IL-4, IL-5, IL-10, IL-13, and IFN-γ were quantified by EIA on stored plasma samples. Primary and secondary antibody pairs (Pharmingen) were used according to the manufacturer's instructions. Avidin–horseradish peroxidase was used to detect biotin-labeled secondary antibodies, and dilutions of recombinant human cytokines (Pharmingen) were used as standards. EIA kits were used to measure plasma levels of soluble IL-2 receptor (sIL-2R) (Endogen), the chemokine eotaxin (Pharmingen), and IgE (United Biotech). Optical density readings were interpreted with SOFTmax PRO software (Molecular Devices). Values below the limit of detection were assigned values midway between 0 and the lower limit of detection, for the purpose of analysis.

Intracellular cytokine staining. Mononuclear cells were stained for intracellular cytokines after incubation at 37°C in 5% CO_2 for 3 h in the presence of phorbol 12-myriastate 13-acetate (50 ng/mL) and ionomycin (1 μg/mL), with use of Cytoperm/Cytofix reagents (Pharmingen), according to the manufacturer's instructions. Stimulated mononuclear cells were harvested, washed, and stained for surface markers with use of fluorescein isothiocyanate–conjugated antibodies to CD4, CD8, or CD56 (Becton Dickinson) at 4°C. After

Table 3. Plasma levels of interleukin (IL)–5 and eosinophil counts, in children with measles and in control children without measles.

	Eosinophil count				IL-5			
Parameter, time point	No. of children	Mean, cells/mm^3 (SD)	Median, cells/mm^3 (IQR)	P^a	No. of children	Mean, pg/mL (SD)	Median, pg/mL (IQR)	P^a
≤3 days after rash onset	84	30 (107)	0 (0–0)	.0001	44	145 (174)	15 (15–243)	.01
4-7 days after rash onset	84	128 (278)	0 (0–138)	.001	51	179 (184)	157 (15–280)	.1
8-14 days after rash onset	35	120 (208)	46 (0–130)	.04	19	66 (142)	15 (15–15)	.0001
1-month follow-up	68	177 (214)	114 (0–268)	.7	34	155 (189)	15 (15–293)	.03
Control children	65	226 (324)	124 (0–270)		32	220 (167)	190 (76–321)	

NOTE. HIV, human immunodeficiency virus; IQR, interquartile range.
[a] Comparison with HIV-uninfected control children.

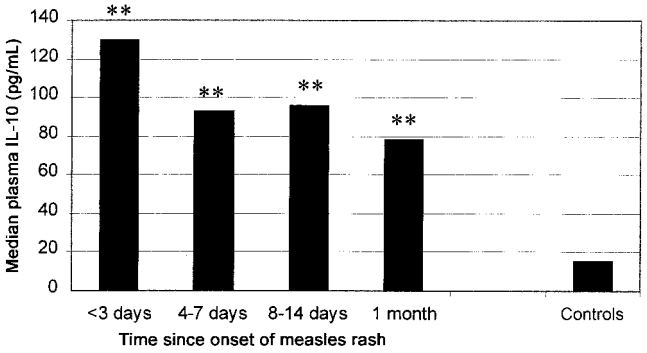

Figure 2. Median plasma interleukin (IL)–10 levels in children with measles and in control children. $^{**}P < .0001$.

being washed and preblocked with equivalent amounts of appropriate isotypes of mouse or rat immunoglobulin at 4°C, cells were permeabilized and stained with phycoerythrin-conjugated antibodies to intracellular IL-4, IL-5, IL-10, or IL-13 (Pharmingen). Flow cytometric analysis on 10^5 cells was done on a FACScan flow cytometer that used Cell Quest software (Becton Dickinson).

Statistical analysis. The Kruskal-Wallis test was used to determine whether measurements for children with measles differed from those of control children. Differences in sex distribution between study groups were compared by the χ^2 test, and differences in median age between study groups were compared by the Kruskal-Wallis test. No formal adjustment was made for multiple testing. Data analysis was done with Stata statistical software (version 6.0; Stata).

Results

Study children. Plasma cytokine assays were done on samples from 161 HIV-uninfected children with measles and 63 HIV-uninfected children without acute illness. Not all cytokine assays were done for all children or at all time points. The median age of the children with measles (18 months; interquartile range [IQR], 9–45 months) did not differ from the median age of control children (21 months; IQR, 10–92 months; $P = .4$). Fifty-five percent of the children with measles and 49% of the control children were boys ($P = .2$). The median number of days of rash at study entry for children hospitalized with measles was 3 (IQR, 2–4 days), the median number of days of hospitalization was 6 (IQR, 5–8 days), and the median number of days from rash onset to the 1-month follow-up visit was 38 (IQR, 36–39 days).

Type 1 cytokines. To assess the production of type 1 cytokines during measles in Zambian children, plasma levels of IFN-γ and sIL-2R were measured (table 1). IFN-γ levels were elevated in children with measles during the first 3 days after rash onset and then returned to control values, whereas sIL-2R levels remained elevated for at least 2 weeks, compared with levels in control children. IFN-γ was detected by intracellular cytokine staining after in vitro stimulation predominantly in $CD8^+$ T lymphocytes and NK cells in the 2 weeks following onset of rash (figure 1). As many as one-third of $CD8^+$ T cells and up to 20% of $CD56^+$ lymphocytes were positive for IFN-γ in the 1–2 weeks following the onset of the rash. In contrast, intracellular IL-2 was detected in a higher proportion of $CD4^+$ T cells after in vitro stimulation. Similar patterns of intracellular cytokine staining were observed when data were analyzed by number of cells rather than percentage (data not shown).

Type 2 cytokines. The genes for IL-4, IL-5, and IL-13 are clustered on chromosome 5 and are frequently coexpressed in conditions associated with activation of Th2 cells [20]. Studies of North and South American children with measles showed a persistent increase in IL-4 as the rash cleared [21]. To determine whether the pattern was similar in Zambian children and whether IL-5 and IL-13 showed patterns similar to IL-4, plasma levels of these cytokines were measured (table 2). IL-4 and IL-13 levels were elevated in children with measles compared with levels in control children. Plasma levels of IL-4 remained significantly higher than control levels at the 1-month follow-up, whereas plasma levels of IL-13 decreased to levels similar to those of control children 1–2 weeks after rash onset. In contrast, plasma levels of IL-5 were lower in Zambian children with measles than in control children at all times after onset of rash (table 3).

IL-4 and IL-13 were detected intracellularly primarily in $CD4^+$ T cells, whereas IL-5 was detected in an almost equal proportion of $CD4^+$ and $CD8^+$ T cells (figure 1). The proportion of $CD4^+$ T cells positive for any of these cytokines was lower than that observed for IL-2.

Eosinophils, IgE, and eotaxin. The type 2 cytokines regulate a number of immunologic functions associated with allergic responses, as well as providing B cell help [22]. Because IL-4 and IL-13 are important regulators of IgE class switching in B cells [23], plasma IgE levels were measured (table 2). Surprisingly, IgE levels were lower in children with measles than in control children. IL-5 is an important regulator of eosinophil production, maturation, and survival [24], so eosinophil counts were also assessed (table 3). As with plasma levels of IL-5, numbers of circulating eosinophils were lower in children with measles than in control children, but they gradually increased to control levels at follow-up. IL-4 induces eotaxin, a chemokine that attracts eosinophils [25], and plasma levels of eotaxin were higher in children with measles during the first week after rash onset (table 2).

IL-10. IL-10 was originally characterized as a factor generated by mouse Th2 cells that inhibited cytokine synthesis by Th1 cells [26]. However, in humans, IL-10 is produced by Th0, Th1, and Th2 cells, as well as a number of other cell types, including macrophages, $CD8^+$ T cells, B cells, keratinocytes, and NK cells [27–31]. IL-10 is a multifunctional cytokine, but primary roles appear to be in the later phases of an immune response for maturation of antibody-secreting B cells and down-regulation of inflammatory processes [31–35]. Plasma levels of IL-10 were el-

evated in children with acute measles and during convalescence (figure 2), and production of IL-10 by T cells was primarily detected in the $CD4^+$ population (figure 1).

Discussion

The present study has shown that immune activation during measles in Zambian children was similar in many respects to that in previously studied US and Peruvian children, and our data support the hypothesis that cytokines induced by measles virus infection may play a role in subsequent immunosuppression. Specifically, sustained high levels of IL-10 during convalescence suggest a role for this immunoregulatory cytokine in measles virus–induced immunosuppression. However, features related to IL-5, eosinophilia, and levels of IgE distinguished these Zambian children from children with measles studied elsewhere. The immune response during measles involved early type 1 responses, with production of IFN-γ predominantly by $CD8^+$ T cells and IL-2 predominantly by $CD4^+$ T cells during the rash phase of the illness. During and after this phase, more-prolonged increases were observed in the type 2 cytokines IL-4 and IL-13, cytokines likely produced by $CD4^+$ T cells, as demonstrated by intracellular staining after in vitro stimulation. IL-5 was produced in vitro by both $CD4^+$ and $CD8^+$ T cells and was regulated differently from IL-4 and IL-13; plasma levels were low in children with measles, compared with the high levels present in control children. Lower levels of IL-5 were reflected in lower eosinophil counts, compared with those in control children. IgE was also lower in children with measles, despite high levels of IL-4 and IL-13.

Each stage in the immunologic response to measles virus is likely to be important in determining the outcome of the measles virus infection and the associated immunosuppression. The rash marks the onset of the immune-mediated clearance of measles virus from multiple sites of replication. Mean plasma IFN-γ levels were elevated only for the 3 days after the onset of the rash. The high level of IFN-γ during the rash is similar to observations in other populations of children with measles, which demonstrated early elevation of IFN-γ prior to rash onset [18]. IFN-γ is a critical participant in type 1 immune responses, because it stimulates macrophage activation and increases expression of major histocompatibility complex class I and II molecules on antigen-presenting cells [36]. IFN-γ was produced primarily by $CD8^+$ T cells and NK cells after stimulation in vitro, which is consistent with the detection of measles virus–specific cytotoxic T lymphocytes in circulation during the measles rash and the proposed role for cytotoxic T lymphocytes in virus clearance [15, 16]. Other studies have shown that activation of $CD8^+$ T cells, as evidenced by production of soluble $CD8^+$ and surface expression of activation markers such as Fas, is greatest during the rash and is quickly down-regulated as virus is cleared and the rash fades [37] (authors' unpublished data). These changes are likely to reflect the rapid expansion and prompt elimination of antigen-specific $CD8^+$ T cells with the decrease in viral antigen, as documented in other acute viral infections [38].

In contrast to $CD8^+$ T cells, $CD4^+$ T cells tend to remain activated for a longer period of time and are presumed to regulate the ongoing maturation of the memory immune response to measles virus. However, differences in the production of type 1 and 2 cytokines by activated $CD4^+$ T cells were apparent. In the acute phase of measles, IL-2, a type 1 cytokine that stimulates proliferation of lymphocytes, was produced primarily by $CD4^+$ T cells after in vitro stimulation, and sIL-2R, a component of the α-chain of the IL-2 receptor, was released from the surface of proliferating cells. Studies elsewhere have shown that plasma levels of IL-2 are elevated for 10–12 days after onset of rash [21]. As observed in the present study, levels of sIL-2R decline somewhat more slowly, which is consistent with the longer half-life of sIL-2R compared with plasma IL-2.

Plasma levels of the type 2 cytokines IL-4 and IL-13, produced primarily by $CD4^+$ T cells, also increased in children with measles. Studies elsewhere have shown elevations of plasma IL-4 for at least 7 weeks after onset of rash in some children [21], and, in the present study, mean plasma IL-4 was increased for at least 5 weeks, although not in all children. High levels of IL-4 are produced by cultured peripheral blood mononuclear cells from children with measles, and antibody to IL-4 improves lymphoproliferative responses, suggesting a role for IL-4 in immunosuppression [21]. IL-13 shares a number of functions with IL-4 but has not previously been studied in measles. Both cytokine receptors use the IL-4R α-chain [39], decrease cytokine production by monocytes, and increase IgE synthesis and eotaxin production [40, 41]. Despite the elevation of IL-4 and IL-13 during measles and the ability of measles virus to synergize with IL-4 to induce IgE production in vitro [42, 43], IgE levels were suppressed in Zambian children with measles compared with those in control children. In previous studies of Peruvian children with measles, plasma IgE levels were elevated during the few days before and for at least 1 week after the onset of rash [42].

In contrast to IL-4 and IL-13, plasma levels of IL-5 were decreased in children with measles compared with those in control children, at essentially all time points examined. Although these 3 cytokines are often expressed together, pathways for selective expression have been identified [44–48]. IL-5 is produced by both $CD4^+$ and $CD8^+$ T cells [49] and can also be expressed by NK cells [50]. IL-5 is an important regulator of eosinophil production and survival [51, 52] and is clearly linked with eosinophilia in helminth infections [53]. In mice, IL-5 promotes B cell proliferation and differentiation and IgE class switching [54] but whether IL-5 plays a role in human B cell maturation remains controversial. Therefore, lower eosinophil counts in Zambian children with measles are consistent with the lower levels of IL-5 that were present, but they differ from previous observations during measles in humans and experimentally infected macaques. The only previous published study

of plasma IL-5 levels in acute measles failed to detect measurable levels of either IL-5 or IL-4 in 9 of 10 patients [55]. However, in addition to increased IL-4 [21], we have also observed elevated plasma IL-5 levels in Peruvian children with measles for 2 weeks following rash onset (unpublished data).

In comparing Zambian with Peruvian children, the major differences appear to be in the levels of IgE, IL-5, and eosinophils. Mean control levels of IgE were 154 IU/mL in Zambian children, and control levels of IL-5 were 220 pg/mL. These data suggest that children in Zambia have high baseline levels of IgE, IL-5, and eosinophils and that measles virus or the immune response to measles virus suppresses these previously high levels. This is further suggested by the fact that, in children with measles, levels of IgE, IL-5, and eosinophils rise toward control values after recovery. The most likely explanation for these high control levels would be chronic helminth infection in Zambian children. Preliminary studies suggest that *Ascaris* infection is common in Zambian children (unpublished data), as it is in other sub-Saharan African populations [56].

The depressed eosinophil counts and plasma IgE and IL-5 levels in Zambian children with measles may be due in part to the immunoregulatory effects of IL-10 [57, 58]. Plasma levels of IL-10 remained elevated for weeks in Zambian children with measles. IL-10 can accelerate eosinophil death by suppressing production of factors that are critical to eosinophil survival, such as granulocyte-macrophage colony-stimulating factor [59]. IL-10 inhibits IL-5 production by T lymphocytes costimulated through CD28 [60–62] and inhibits IL-5 production in several mouse models of allergic disease [63, 64]. In addition, IL-4–induced synthesis of IgE can be prevented by IL-10 [65–67], and IL-10 has been hypothesized to play a critical role in the decreased prevalence of atopy among persons with chronic helminth infections [68, 69].

The primary cellular source of IL-10 and the means of its induction during measles are not clear. Monocytes and macrophages are an important source of IL-10, and production in vitro is directly induced by viruses that infect macrophages, such as HIV, rhinovirus 14, respiratory syncytial virus, parainfluenza virus type 3, and murine cytomegalovirus [70–76]. Few studies have measured IL-10 levels in vivo following acute viral infection. Plasma or serum IL-10 levels are increased during persistent infection with hepatitis C virus [77], transiently increased in rubella and influenza virus infections [78, 79], and increased for 10 days after rash onset in Japanese children with measles [80]. Because measles virus infects monocytes and macrophages [10, 11], IL-10 could be directly induced by measles virus infection. Stimulation of monocytes in peripheral blood from measles patients in The Gambia did not show an increase in IL-10 secretion, compared with control subjects [81], but the relevant monocytes and macrophages are probably in tissue. Alternatively, the immune response to measles virus may result in increased IL-10 production by cells not directly infected. Small numbers of $CD4^+$ T cells were positive for intracellular IL-10, but these cells are unlikely to be the primary source of IL-10 in these children.

The synthesis of IL-10 is likely to be important for development of the sustained high-quality antibody response that characteristically accompanies recovery from measles. IL-10 enhances B cell proliferation, prevents the death of germinal center B cells, and induces B cell differentiation into antibody-secreting cells [32, 82]. However, IL-10 is also broadly immunoregulatory and immunosuppressive. IL-10 down-regulates the synthesis of a wide array of cytokines, suppresses macrophage activation, suppresses T cell proliferation, and promotes the release of cytokine inhibitors [29, 33, 73, 83–85]. IL-10 has been linked to a shift from type 1 to type 2 responses in chronic murine schistosomiasis [86] and to virus-induced immunosuppression [87]. In fact, some herpesviruses produce a virally encoded IL-10 that may suppress antiviral immune responses [88, 89]. IL-10 could account for many of the manifestations of immunosuppression observed during and after measles [4, 5]. IL-10 inhibits delayed-type hypersensitivity responses [90, 91] and T cell proliferation to mitogens [92, 93] and increases susceptibility to other infections by impairing macrophage function [94–97].

We report several novel observations concerning cytokine responses during measles virus infection. The findings suggest that plasma levels of IL-5, IgE, and eosinophils are regulated differently in Zambian children than in previously studied American or Peruvian children, perhaps because of nutritional deficiencies or concurrent infections. We also observed high plasma levels of IL-10, potentially contributing to the impaired cellular immunity and depressed hypersensitivity responses that follow measles.

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