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Clinical and immunological analysis of measles patients admitted to a Beijing hospital in 2014 during an outbreak in China

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SUMMARY

At the end of 2013, China reported a countrywide outbreak of measles. From January to May 2014, we investigated the clinical and immunological features of the cases of the outbreak admitted to our hospital. In this study, all 112 inpatients with clinically diagnosed measles were recruited from the 302 Military Hospital of China. The virus was isolated from throat swabs from these patients, and cytokine profiles were examined. By detecting the measles virus of 30 of the 112 patients, we found that this measles outbreak was of the H1 genotype, which is the major strain in China. The rates of complications, specifically pneumonia and liver injury, differed significantly in patients aged <8 months, 8 months to 18 years, and >18 years: pneumonia was more common in children, while liver injury was more common in adults. Pneumonia was a significant independent risk factor affecting measles duration. Compared to healthy subjects, measles patients had fewer $CD4^+IL\text{-}17^+$, $CD4^+IFN\text{-}\gamma^+$, and $CD8^+IFN\text{-}\gamma^+$ cells in both the acute and recovery phases. In contrast, measles patients in the acute phase had more $CD8^+IL\text{-}22^+$ cells than those in recovery or healthy subjects. We recommend that future studies focus on the age-related distribution of pneumonia and liver injury as measles-related complications as well as the association between immunological markers and measles prognosis.

Key words: Cytokine, H1 genotype, liver injury, measles, pneumonia.

INTRODUCTION

Measles, also known as morbilli, rubeola, or red measles, is a highly contagious acute respiratory infection caused by the measles virus. Although most patients are cured within 3 weeks, some may develop complications such as pneumonia, enteritis, encephalitis, and liver injury [1, 2]. Complications from measles can occur in almost every organ system, and the most common causes of death are pneumonia, croup, and encephalitis [3]. With the implementation of the global measles eradication programme, the incidence of measles and related mortality has declined significantly in recent years. However, the situation in many developing countries remains challenging, particularly where endemic measles strains persist. Measles continues to cause morbidity and death in children worldwide. In 2014, there were 114 900 measles deaths globally – about 314 deaths every

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day or 13 deaths every hour (http://www.who.int/mediacentre/factsheets/fs286/en/). In China, 596 391 cases of measles and 368 measles-related deaths were reported from 2005 to 2013 [4]. From 1978, China began to carry out measles vaccination for 8-month-old infants. Starting in 1986, a second dose of measles vaccine was administered to 7-year-old children. From 2004, the implementation of the second dose of measles vaccine was administered to infants aged 18–24 months.

Although measles vaccines have been introduced, this disease may occur even in vaccinated individuals, and indigenous measles strains continue to circulate in China. In fact, a resurgence of measles occurred in Beijing at the end of 2013. To achieve the end of the measles epidemic, it is very important to characterize the clinical and immunological features of measles. Here, we report a clinical and immunological analysis of 112 cases of measles at the 302 Military Hospital of China, which is the largest hospital in China specializing in infectious disease and the centre for measles treatment in the Beijing district.

METHODS

Patients

Patients with a clinical diagnosis of measles at the 302 Military Hospital of China between January and May 2014 were prospectively recruited. Diagnosis was conducted in accordance with the WS 296-2008 guidelines (measles diagnostic criteria by Centers for Disease Control of China) according to typical clinical manifestations, such as fever, rash, upper respiratory catarrh, conjunctivitis, and oral Koplik spots with epidemiological features. Written informed consent was obtained from all patients. Patient consent was obtained for their blood and swab samples to be used for immunological and virological analyses.

Flow cytometry

For comparison of cytokine levels, 30 measles patients who agreed to donate an additional blood sample for immunological analysis and 30 sex- and age-matched healthy individuals without any infectious disease were enrolled. Blood was collected in the acute (2–3 days after maculopapular eruption) and recovery (3–4 days after fever subsided) phases. APC-Cy7-conjugated anti-CD3, FITC-conjugated anti-IFN-γ, and PerCP-conjugated anti-CD8 were purchased from BD Biosciences (USA); phycoerythrin (PE)-conjugated anti-IL-22 and APC-conjugated anti-IL-17A, from eBioscience (USA); and PE-Cy7-conjugated anti-CD56 from Biolegend (USA). For intracellular cytokine staining, fresh heparinized peripheral blood (200 µl) was stimulated using PMA (50 ng/ml; Sigma, USA) and ionomycin (1 µg/ml, Sigma) in 800 µl RPMI 1640 medium supplemented with 10% fetal bovine serum, followed by incubation with 10 µg/ml Brefeldin A (Sigma) for 6 h. After surface markers were stained, the cells were washed, lysed, fixed, permeabilized utilizing a commercially available kit (eBioscience), stained with the corresponding intracellular antibodies, and analysed by multicolour flow cytometry using FACSAria and FlowJo software (Tristar, USA).

Virus antibody detection and RNA isolation and sequencing

Blood samples were collected from all patients for measles antibody detection. The measles IgM was measured by enzyme-linked immunosorbent assay using the anti-measles virus ELISA (IgM) (EUROIMMUN Medical Laboratory Diagnostics Stock Company, Germany).

Throat swabs were collected from the 30 patients in the acute phase of infection for virus isolation and sequencing. Viral RNA was extracted from these samples using a DP315-R kit (Tiangen, China). Nested reverse transcription–polymerase chain reaction (RT–PCR) was then performed using a TaKaRa One-Step RNA PCR kit and TransStart FastPfu DNA Polymerase (AP221; TransGen Biotech Co. Ltd, China). The product of the second round of PCR with the target band was sequenced using the MZ-R primer (Shenggong, China). The reference strain used to determine the primer locations was from GenBank (sequence FJ416068, Changchun, China). Five microlitres of PCR product was resolved via electrophoresis in 1% agarose gel. The results were compared to the measles virus sequence on the NCBI website using BLAST analysis. The PCR primers are shown in Table 1.

Statistical analysis

Data were deposited in EpiData software (http://www.epidata.dk/) via double entry. They were analysed using SAS software (version 9.1.3; SAS Institute Inc., USA). For single-factor one-way analysis of variance, we chose the standard alpha (α) = 0·05 criterion. The disease course was defined as the period from the

Table 1. *Primers used for nested PCR amplification*

	Direction	Sequence (5′→3′)	Site of the primers	Product size (bp)
First round	Forward	AGAAAATGGTTGGATGTGGTGAG	744–766	1201
	Reverse	GCTCCTGTCCTGGGTTGTCTGAT	1923–1945	
Second round	Forward	GCTATGCCATGGGAGTAGGAGTGG	1108–1131	593
	Reverse	CCTCGGCCTCTCGCACCTAGT	1681–1701	

start of fever to cure and discharge. Cox proportional hazards analysis was used to analyse disease course on the basis of different baseline covariates, e.g. sex, age, alanine aminotransferase (ALT) levels, highest body temperature, white blood cell (WBC) count, and complications. The α value was set at 0·1 (two-sided test). $P < 0·05$ was considered statistically significant.

Ethical statement

The Ethics Committee of our hospital approved this prospective study.

RESULTS

General information regarding the 2014 measles outbreak

During the 2014 measles outbreak in Beijing, 112 measles patients were admitted to our hospital (54 male). The median age was 27·5 years (range 3 months to 78 years). Of these, 13 (11·61%) were aged <8 months, 14 (12·5%) were aged between 8 months and 18 years, and 85 (75·89%) were aged >18 years; the median ages in these groups were 0·58, 2·5, and 31 years, respectively. Hospitalization duration ranged from 1 to 11 days (mean 4·66 ± 1·86 days). Maculopapular eruption time ranged from within 24 h to 9 days (mean 3·07 ± 1·53 days) after fever development. Body temperatures ranged from 38·3 °C to 42 °C (mean 39·52 ± 0·63 °C), and the duration of fever ranged between 2 and 14 days (mean 7·33 ± 2·26 days). Last, 88 (78·57%) of the 112 patients had oral Koplik spots (Table 2).

Table 2. *Clinical characteristics of enrolled subjects*

Subjects, *n*	112
Age, years (median, quartile)	
Total	27·5 (19·2–35·0)
<8 months	0·58 (0·42–0·67)
8 months to 18 years	2·5 (0·88–6·50)
>18 years	31·0 (19·3–35·0)
Sex, *n* (M/F)	54/58
Age group, *n*	
<8 months	13
8 months to 18 years	14
>18 years	85
Serum anti-measles virus antibody, *n*	
Positive	101
Negative	11
WBC count, $\times 10^9$/l	6·79 ± 5·90
Neutrophil count, $\times 10^9$/l	4·20 ± 3·43
Lymphocyte count, $\times 10^9$/l	2·86 ± 2·08
Platelet count, $\times 10^9$/l	186·09 ± 93·51
Complications, *n*	
Pneumonia	37
Liver injury	56
Enteritis	28
Fever duration, days	7·33 ± 2·25
Number of hospital days	4·66 ± 1·86

WBC, White blood cell

Biochemical indicators

Among the 112 measles patients, 27 showed a lowered WBC count, while 12 showed an increased count during the acute phase. One hundred and one patients tested positive for IgM rubeola antibodies, but there was no significant difference regarding sex ($P = 0·2832$). Abnormal liver function as measured by ALT is defined as ALT >40 U/l, ALT between 40 and 79 U/l indicates mild injury, 80–400 U/l indicates moderate injury, and ALT >400 U/l means severe injury. We showed that 56 patients had liver injury as a complication, as evidenced by increased ALT levels. Further, the liver injury rates differed significantly in the three age groups ($P = 0·0011$).

Sequencing

The virus RNA was detected by PCR from throat swab samples of 30 of the 112 patients; 26 (86·7%) of these 30 patients tested positive. The PCR products formed a ~593-bp band, which was the expected size of the amplification products. The 450-bp sequence at the C-terminal of the nucleoprotein (N) gene of the measles virus was then sequenced and compared with 24 known measles virus genotypes. All the

Table 3. *Multivariate analysis of risk factors for pneumonia*

	Pneumonia	No pneumonia	*t*	χ^2	*P*
Sex, M/F	18/19	36/39	–	0·004	0·554
Age, years	19·51 ± 19·25	28·71 ± 12·89	−2·632	–	0·011
Age group, *n*					
<8 months	10	3	–	12·805	0·001
8 months to 18 years	8	6	–	4·203	0·043
>18 years	19	66	–	18·189	0·000
Fever duration, days	8·27 ± 2·19	6·87 ± 2·16	3·220	–	0·002
WBC count, 10^9/l	9·930 ± 9·125	5·251 ± 2·099	3·079	–	0·004
Neutrophil count, %	60·38 ± 19·84	65·75 ± 19·05	−1·384	–	0·169
ALT level range, *n*					
<40	24	33	–	4·316	0·030
40–79	5	18	–	1·670	0·148
80–400	8	22	–	0·751	0·264
>400	0	2	–	1·005	0·446
Koplik spots positive	29/8	59/16	–	0·001	0·577
Measles antibody positive	37/0	64/11	–	6·018	0·009
Enteritis, *n*	9/28	19/56	–	0·013	0·551

WBC, White blood cell; ALT, alanine aminotransferase.

measles virus isolates from the outbreak cases were of the H1 genotype with a base coincidence rate of ⩾98·2% and showed the highest homology with the Jiangxi strain, which is the current epidemic strain of the measles virus in China.

Pneumonia

Thirty-seven patients developed measles-associated pneumonia (33·04%, Table 3). The percentage of measles patients who developed pneumonia did not differ significantly regarding sex ($P = 0·9485$) but it did differ significantly in the three age groups ($P < 0·001$).

Multivariate analyses

A multiple linear regression model was then applied to identify variables that were significant in independently predicting the disease course (Fig. 1), and pneumonia was found to be one such factor ($P < 0·0001$).

Immunological characteristics of measles patients

Immunological features were compared between 30 of the 112 measles patients and 30 age- and sex-matched healthy subjects, who were selected as the control group (Table 4). The percentage of $CD3^+$ T cells was significantly lower in the acute phase of measles patients than in the recovery phase of measles patients and controls ($P < 0·05$). The measles patients had significantly fewer $CD4^+IL\text{-}17^+$ cells ($P < 0·01$), $CD4^+IFN\text{-}\gamma^+$ cells (Fig. 2), and $CD8^+IFN\text{-}\gamma^+$ cells than healthy subjects ($P < 0·05$). However, they had more $CD8^+IL\text{-}22^+$cells in the acute phase than in the recovery phase and had more of these cells than control subjects ($P < 0·05$).

DISCUSSION

In the present study, 112 measles patients were clinically evaluated, and 101 tested positive for measles antibody. However, the typical clinical manifestations of measles were also observed in the 11 remaining patients who tested negative for the antibody. We speculate that the IgM negative response in some measles patients may due to the sensitivity of the detection kit and the low titre of the measles antibody. Our clinical findings are in agreement with those observed in a previous study [5].

Moreover, the complications noted in the present study were also similar to those reported previously [6], i.e. liver injury (50%), pneumonia/bronchopneumonia (33·04%), and enteritis (25·0%). The significant differences in liver injury in the three age groups in the present study indicated that this complication correlated positively with age. All measles patients enrolled in this study had no alcoholism-, infection- or drug-related liver diseases. Although the exact underlying mechanism(s) remain unclear, the use of antipyretics in treating measles infection may be a

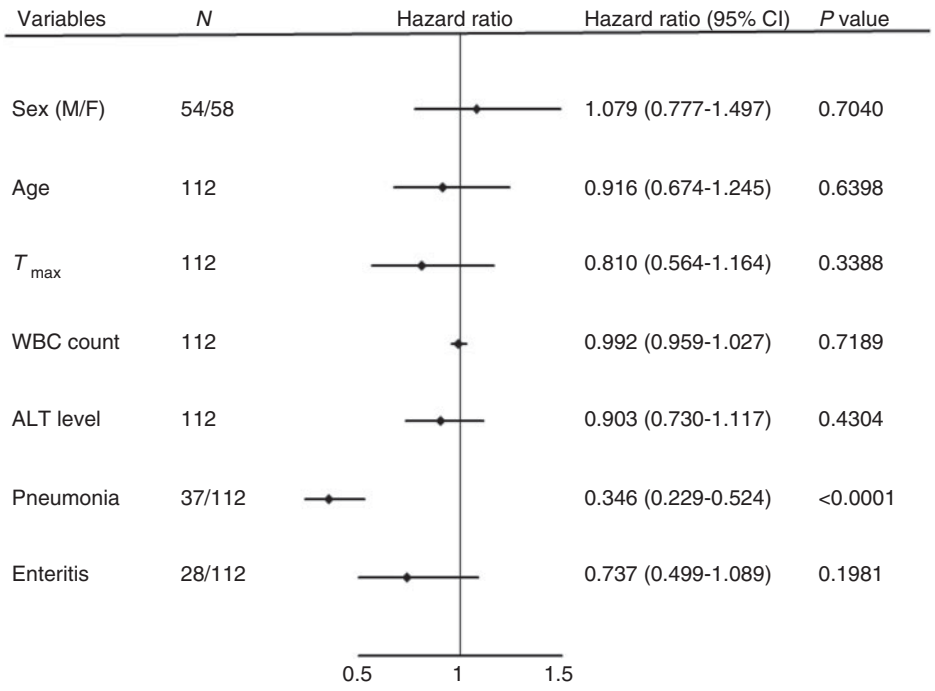

Fig. 1. Cox analysis of independent risk factors related to measles infection. The disease course of measles was defined as the period from the start of fever to cure and discharge. Cox proportional hazards analysis was used to calculate the disease course on the basis of different baseline covariates, namely, sex, age, alanine aminotransferase (ALT) level, highest body temperature (T_{max}), white blood cell (WBC) count, and complications (pneumonia and enteritis); α was set at 0·1 (two-sided test). $P < 0{\cdot}05$ was considered statistically significant.

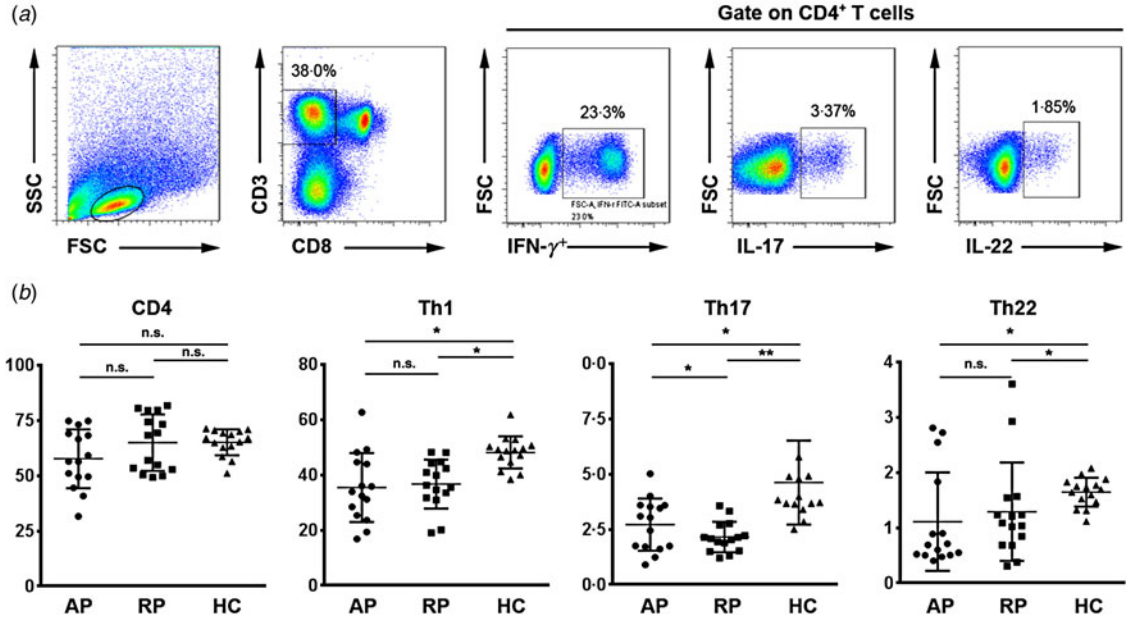

Fig. 2. Measles patients had significantly fewer IL-17$^+$ cells, IFN-γ^+ cells, and IL-22$^+$ cells than healthy subjects. (*a*) Freshly isolated peripheral blood mononucleocytes were gated from total peripheral leukocytes on the basis of their forward and side scatter, and CD4$^+$ T cells were identified as CD3$^+$CD8$^-$ T cells. IL-17$^+$, IFN-γ^+, and IL-22$^+$ cells were gated from the CD4$^+$ T cells. (*b*) Statistical analysis of distribution of the total population of CD4$^+$ T cells, Th17 cells (IL-17$^+$CD4$^+$ T cells), Th1 cells (IFN-γ^+CD4$^+$ T cells), and Th22 cells (IL-22$^+$CD4$^+$ T cells) in patients and healthy controls. AP, Acute phase; RP, recovery phase; HC, healthy control.

Table 4. *Lymphocyte subpopulations in measles patients and healthy subjects (%)*

	Group		Mean difference			
	I	J	I – J†	S.E.	*P*	95% CI
CD3/Lym	AP	RP	−11·24000*	4·47090	0·016	−19·2626 to –20·2626
	AP	HC	−10·24000*	4·47090	0·027	−10·0226 to –2·2174
	HC	RP	−1·00000	4·47090	0·824	−15·4726 to –1·2174
CD4/CD3	AP	RP	−7·26667	4·06619	0·081	−15·6126 to 8·0226
	AP	HC	−7·40667	4·06619	0·076	−8·0659 to 0·9392
	HC	RP	0·14000	4·06619	0·973	−0·7018 to 0·7992
$CD8^+/CD3^+$	AP	RP	7·45333	4·04102	0·072	−0·8018 to 8·3459
	AP	HC	7·35333	4·04102	0·076	−8·0551 to 15·6084
	HC	RP	0·10000	4·04102	0·980	−0·4338 to 15·5084
$CD4^+IL\text{-}17^+/CD4^+$	AP	RP	0·56160	0·49322	0·261	−2·8954 to 8·2551
	AP	HC	−1·90007*	0·49322	0·000	1·4663 to 1·5570
	HC	RP	2·46167*	0·49322	0·000	−8·1819 to –0·9047
$CD4^+IFN\text{-}\gamma^+/CD4^+$	AP	RP	−1·22580	3·44688	0·724	−19·6828 to 3·4570
	AP	HC	−12·72667*	3·44688	0·001	4·5448 to 5·7303
	HC	RP	11·50087*	3·44688	0·002	−7·3239 to –5·7706
$CD4^+IL\text{-}22^+/CD4^+$	AP	RP	−0·18073	0·27071	0·508	−0·8367 to 0·4752
	AP	HC	−0·53433	0·27071	0·0552	−1·7236 to –0·4117
	HC	RP	0·35360	0·27071	0·199	0·2310 to 1·5429
$CD8^+IFN\text{-}\gamma^+/CD8^+$	AP	RP	3·26520	4·47413	0·470	−22·8625 to 18·4570
	AP	HC	−12·27333*	4·47413	0·009	6·2827 to 11·1877
	HC	RP	15·53853*	4·47413	0·001	0·0717 to –4·3509
$CD8^+IL\text{-}22^+/CD8^+$	AP	RP	0·28893*	0·12125	0·022	0·2976 to 24·7943
	AP	HC	0·54147*	0·12125	0·000	−0·4697 to 0·5595
	HC	RP	−0·25253*	0·12125	0·043	−0·8367 to 0·7853

S.E., Standard error; CI, confidence interval; AP, acute phase; RP, recovery phase; HC, healthy control.
† Mean difference between the I and J groups.
*$P < 0·05$.

possible cause that requires further investigation. In a study by Ackerman *et al.* [7], 56% of 118 measles patients had various degrees of liver damage, and the incidence was substantially higher in patients using acetaminophen (a well-known medication that may lead to liver damage) as an antipyretic than in those using metamizole. Further, liver protective treatment with compound glycyrrhizin injections reversed the liver damage, and severe complications such as liver failure did not occur.

In the present study, we found that younger patients had a higher chance of developing pneumonia and that pneumonia was an independent risk factor that influenced the disease course. Severe respiratory complications have previously been reported to be significant independent risk factors for mortality in children with measles [8]. Pathological studies of children who died with acute measles found multinucleated giant cells typical of measles virus infection throughout the respiratory and gastrointestinal tracts and in most lymphoid tissues [3]. Therefore, lung imaging is highly recommended for children with respiratory symptoms, to check for possible pulmonary inflammatory lesions and to administer timely and proper treatment. Further, in rural areas or districts with poor nutritional conditions and hygiene, children with measles need extra care, to prevent pneumonia.

Measles virus infection is known to cause severe immunosuppression, which contributes to many related complications [9]. The immunosuppressive state can last from several weeks to several months [10], and the pathogenicity of measles is related to the immune status of the infected individual. It has been shown that measles leads to a decline in CD4 lymphocytes, dysfunction of cellular immune response, and reduced proliferation of lymphocytes [11]. In the present study, we found that the number of $CD3^+$ cells was significantly reduced in the acute phase of measles virus infection but returned to normal level after recovery, and the percentages of $CD4^+$ and $CD8^+$ cells, which produce IFN-γ, were reduced during the disease course. These results are consistent with those of a

previous study showing that measles changes the T helper 1 and T helper 2 cytokine balance, thereby enhancing T helper 2-mediated responses [11]. Another study showed that children with acute measles infection had considerably impaired cellular immune function [12]. Further, in adult patients, the percentages of $CD3^+$ and $CD4^+$ T cells were found to be significantly reduced [13]. We also found that the percentages of $CD4^+$ cells that produce IL-17 were also decreased during acute measles infection. Cytokine IL-17 is crucial to the innate and adaptive arms of the immune system. IL-17A was initially reported to be mainly expressed by activated $CD4^+$ T cells, which fight against pathogen invasion at different phases and locations of infection [14]. Given the important role of IFN-γ in combating viral and bacterial infections and that of IL-17 in mediating both innate and cellular immune responses, the reduction in the number of IL-7-producing $CD4^+$ cells may be responsible for the immunosuppression observed in measles infection and be associated with the complications observed during the disease course.

In the acute phase of measles, the percentage of $CD8^+$ T cells that produced IL-22 was higher than that in recovering patients or control subjects ($P < 0{\cdot}05$) in the present study. IL-22 modulates tissue responses during inflammation and promotes antimicrobial immunity and tissue repair at barrier surfaces by binding to the IL-22R receptor. This cytokine can trigger pro-inflammatory and antimicrobial responses to clear pathogens. Recently, IL-22 was found to be essential for lung epithelial repair after influenza [15]. It was initially thought to be produced by $CD4^+$ T cells, but recent studies have shown that $CD8^+$ T cells in psoriatic lesions are an important source of IL-22 [16, 17]. Thus, the increased proliferation of $CD8^+$ T cells that produce IL-22 during acute infection suggests that these cells play an important role in the control of measles infection. Additionally, they may also contribute to tissue repair during recovery.

This study has some limitations. We identified a high prevalence of pneumonia in children with measles and liver damage in adults. However, we were unable to determine the causes underlying this age-related distribution of complications. Further, immunological analysis was not conducted for all patients since blood samples were not available. Therefore, we were not able to investigate the association between immunological markers and disease prognosis. In addition, the patients enrolled in this study are those that were admitted to our hospital, whose illness may be more serious, and are not representative of all measles cases.

In conclusion, the measles virus in our study was the H1 genotype, the dominant epidemic strain in China, suggesting it remains controllable using the current measles vaccines. The clinical manifestations are the same as those of typical measles. However, diagnosis and treatment should pay attention to complications such as paediatric pneumonia and adult liver injury. Measles infection alters the host immune response with decreased IFN-γ and IL-17 production, which may lead to immunosuppresseed status. A better understanding of the immunological profiles of measles infection may further our understanding of its pathogenesis.

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DECLARATION OF INTEREST

None

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