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COMMENTARY
The lack of protective immunity against RSV in the elderly

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Respiratory infections have long been known to lead to severe, sometimes life-threatening, clinical complications in the very young and the old. They are the fourth most common cause of death in the elderly (www.who.org). Most respiratory pathogens can re-infect people who have suffered from them earlier in life and they thus remain a threat throughout the human lifespan.

Respiratory infections can be induced by several classes of pathogen; bacteria, fungi, and mainly, viruses. However, laboratory diagnostic methods have in the past frequently failed to identify a pathogen. Consequently, it was frequently assumed in those cases where the aetiology remained unclear that the pathogens were viral. In fact, since 2001 and starting with human metapneumovirus [1], an increasing number of respiratory viruses have been identified by novel virus discovery approaches, closing the gap left by unclear aetiologies. Most of these viruses have been shown to infect young children.

Meanwhile, there have been several reports clearly showing that other patient cohorts, often neglected regarding respiratory infection, also suffer from severe respiratory infections caused by viruses. These are sometimes even more severe than in children [2–6] and have often been investigated solely for influenza and SARS [6–8]. In contrast, reports on other viruses that occur in practice every day are rare [2–6].

One major group severely affected by respiratory infections is the elderly population that is assumed to suffer from immunosenescence. Immunosenescence is defined as dysfunctional immunity in the elderly [9] and is mainly characterized by perturbations of the T-lymphocyte system. Manifestations of immunosenescence are the 'increasing frequencies of cells previously exposed to an antigen … and decreasing frequencies of cells able to recognize and [successfully] combat sources of new antigens' [9].

Hitherto, despite investigation over more than 25 years, there remains confusion in the clinical and basic definitions of immunosenescence and the parameters that are affected by immunosenescence [10]. It also appears that immunosenescence itself, despite being a part of the normal ageing process, is recognized as a clinical entity rather than a natural process. The reason for this may be that immunosenescence is suspected to have an infectious component. In the past it was noted that the elderly tended to have oligoclonal expansions of CD8+ T cells that are accompanied by an increasing seroprevalence of human cytomegalovirus (CMV). Thereby, CMV was shown to be the driving force behind most of those oligoclonal T-cell expansions and led to altered phenotypes and functions of the affected cell populations [10]. The hypothesis of Pawelec and colleagues [9, 10] that immunosenescence has an infectious component is independently supported by a Swedish study that showed that a so-called immune risk phenotype (IRP) that predicts higher mortality rates is strongly associated with CMV seropositivity [11–13]. As an additional problem it appears that the mucosal immunity, the first barrier against respiratory pathogens, becomes less effective with age as characterized for example by lower IgA secretion [14]. In concert with an infectious component as hypothesized by Pawelec and colleagues [9, 10] the mature but less flexible immune system of the elderly invites new, emerging, highly variable, or re-emerging pathogens

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to attack them, so that they are predisposed to become severely ill in consequence.

From these points of view, the report by Terrosi and colleagues is important [15]. They show that severe infections with respiratory syncytial virus (RSV) in the elderly may be caused by the lack of neutralizing antibodies against this pathogen. They tested a large number of sera collected from age groups of adults ranging from 20 years to >80 years, the latter group with a mean age of 83·70 years. Terrosi and coworkers state that the lack of neutralizing antibodies can be caused by immunosenescence, i.e. the lack of ability to respond to a specific antigen or to (re)-activate an immune response, or by lack of a (recent) exposure to the virus [15].

Taking into account the epidemiology of RSV that is spread worldwide and occurs throughout the whole year with seasonal waves in winter, the latter assumption is possible but unlikely. Most of the elderly probably have contact with their grandchildren, who in turn are most likely to be the group in whom RSV circulates the most. More likely is the hypothesis that the elderly's immune system becomes as frail as the rest of the human body and is unable to fight viruses that have an evolution rate as high as those of RNA viruses. The virus that infects an elderly person may be significantly different from the variant that infected the same person at a lower age.

Most recent developments in the pandemic of the novel swine-originated H1N1 influenza show that in that case it is not the elderly but the younger adult patient cohort that suffers from the most severe infections (www.who.org [16, 17]). Taking the immunosenescence concept as a basis one had to assume that it is the elderly who are most affected by this new wave of respiratory viruses, but in fact in the first instance this is not true, making additional currently unknown factors likely contributors to the clinical course. In turn, those recent developments that the elderly are less affected by the novel challenge by H1N1 of swine origin may lead to the interpretation that ageing effects may have an opposite, i.e. protective, effect. However, it is hoped that the current influenza wave is not a 'harmless' prelude to a second severe outbreak later in the influenza season.

The Terrosi group further remind us that:

> RSV-specific T-cell response plays a major role in the clearance of the virus and in the clinical outcome of RSV infection … neutralizing antibodies, are necessary for maintaining protective immunity in the host [15].

As a consequence of those observations and conclusions the next step in research has to be the evaluation of the RSV-specific CTL memory, i.e. the CD127+ T cell, a T-cell subpopulation that may persist for long time even in the absence of specific antigen activation. It can be speculated from the data presented by the Terrosi group that the memory T-cell response in the oldest cohort of patients will be lowest and that those elderly individuals with the best RSV-specific CD8+ memory can reactivate a sufficiently rapid antibody response.

Previous studies have shown that virtually all adults have antibodies against RSV [6, 18, 19]; thus the data of the Terrosi group are surprising as it remains unclear why the elderly suffer from life-threatening RSV infections [15]. The data lead to the hypothesis that either immunosenescence, or viral evolution followed by immune escape, or a combination of both, occurs in severe cases of RSV infections in the elderly. This concept is not really new, but so far has been hypothesized solely for influenza viruses, although also observed in the SARS epidemics. Unfortunately, those extreme events, i.e. the SARS epidemics, the annual influenza wave, and the media-driven bird flu panic have led to an imbalance in research focus and funding. The data from Terrosi *et al.* [15] show that it is not only the 'new' viruses but also long known pathogens that are of importance in the elderly cohort. The impact of RSV, although known for decades, is still underestimated in the elderly, although recent data show its importance [20]. This is also true for parainfluenza viruses [21] and, as a recent report shows, for human metapneumovirus, the latter being clinically indistinguishable from RSV and parainfluenza viruses. These viruses are also distributed worldwide but only rarely detected in elderly individuals, mainly because they are not looked for in this cohort, but they can lead to severe outbreaks with lethal outcome [22].

Worldwide, more money seems to be available for research on a thus far hypothetical outbreak of bird flu or for research on SARS coronaviruses than for research on pathogens assumed to be 'harmless', even though the latter kill patients in all age groups every year.

Surprisingly, and paradoxically, whilst most of the scientific and lay community expected an H5N1 outbreak and a pandemic originating in Asia, the Mexican swine flu evolved and resulted in a worldwide distribution of the virus with, thus far, fewer severe clinical cases than expected for a novel flu strain.

In the elderly it is also less severe than the majority of respiratory infections observed daily, possibly due to a long immune memory effect in those patients who experienced previous H1N1 waves in the past.

The paper by Terrosi and co-workers [15] should be seen as a reminder of the real danger and is a basis for studying the concept of severe respiratory infections in the elderly. In the future, more integrated research linking studies of an interdisciplinary nature are required to address the condition of immunosenescence and to respond to the upcoming challenges emerging pathogens will bring. Furthermore, greater efforts for the prevention of those epidemic infections, e.g. stricter hygiene and isolation of affected patients, are needed. Despite the risk of local economic damage, daring to stop airway travel for a short period in cases when outbreaks occur should also be considered, not least as the economic consequences of a global pandemic are far from being calculable.

Fortunately, the importance for the elderly of viral respiratory infections other than influenza was most recently discussed at an international meeting in Seville in March 2009. This was organized by the International Society for Influenza & other Respiratory Virus Diseases (www.isirv.org), giving hope for future research approaches. It remains surprising that globally the non-flu viruses remain out of the focus of global (WHO) and local organizations (e.g. health ministries) despite timely reminders and the daily virological and clinical experiences [23].

DECLARATION OF INTEREST

None.

REFERENCES

1. **van den Hoogen BG, *et al.*** A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nature Medicine* 2001; **7**: 719–724.
2. **Bastien N, *et al.*** Human coronavirus NL63 infection in Canada. *Journal of Infectious Diseases* 2005; **191**: 503–506.
3. **Boivin G, *et al.*** An outbreak of severe respiratory tract infection due to human metapneumovirus in a long-term care facility. *Clinical Infectious Diseases* 2007; **44**: 1152–1158.
4. **Simon A, *et al.*** Nosocomial infection: a risk factor for a complicated course in children with respiratory syncytial virus infection – results from a prospective multicenter German surveillance study. *International Journal of Hygiene and Environmental Health* 2008; **211**: 241–250.
5. **Skull SA, *et al.*** Hospitalized community-acquired pneumonia in the elderly: an Australian case-cohort study. *Epidemiology and Infection* 2009; **137**: 194–202.
6. **van der Hoek L.** Human coronaviruses: what do they cause? *Antiviral Therapy* 2007; **12**: 651–658.
7. **Bouree P.** Immunity and immunization in elderly. *Pathologic Biology* (*Paris*) 2003; **51**: 581–585.
8. **Johnstone J, *et al.*** Viral infection in adults hospitalized with community-acquired pneumonia: prevalence, pathogens, and presentation. *Chest* 2008; **134**: 1141–1148.
9. **Pawelec G, *et al.*** Human immunosenescence: does it have an infectious component? *Annals of the New York Academy of Science* 2006; **1067**: 56–65.
10. **Pawelec G, *et al.*** Human immunosenescence: is it infectious? *Immunology Reviews* 2005; **205**: 257–268.
11. **Wikby A, *et al.*** Age-related changes in immune parameters in a very old population of Swedish people: a longitudinal study. *Experimental Gerontology* 1994; **29**: 531–541.
12. **Wikby A, *et al.*** Changes in CD8 and CD4 lymphocyte subsets, T cell proliferation responses and non-survival in the very old: the Swedish longitudinal OCTO-immune study. *Mechanisms in Ageing Development* 1998; **102**: 187–198.
13. **Ferguson FG.** Immune parameters in a longitudinal study of a very old population of Swedish people: a comparison between survivors and nonsurvivors. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 1995; **50**: B378–B382.
14. **Schmucker DL.** Intestinal mucosal immunosenescence in rats. *Experimental Gerontology* 2002; **37**: 197–203.
15. **Terrosi C, *et al.*** Humoral immunity to respiratory syncytial virus in young and elderly adults. *Epidemiology and Infection*. doi:10.1017/S0950268809002593. Published online 15 April 2009.
16. **Novel Swine Origin Influenza A (H1N1) Virus Investigation Team.** Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *New England Journal of Medicine* 2009; **360**: 2605–2615.
17. **Shinde VEA.** Triple-reassortant swine influenza A (H1) in humans in United States, 2005–2009. *New England Journal of Medicine* 2009; **360**: 2616–2625.
18. **Falsey AR.** Respiratory syncytial virus infection in adults. *Seminars in Respiratory and Critical Care Medicine* 2007; **28**: 171–181.
19. **Falsey AR, *et al.*** Long-term care facilities: a cornucopia of viral pathogens. *Journal of the American Geriatric Society* 2008; **56**: 1281–1285.
20. **Hasman H, *et al.*** Aetiology of influenza-like illness in adults includes parainfluenzavirus type 4. *Journal of Medical Microbiology* 2009; **58**: 408–413.
21. **Caram LB, *et al.*** Respiratory syncytial virus outbreak in a long-term care facility detected using reverse transcriptase polymerase chain reaction: an argument for real-time detection methods. *Journal of the American Geriatric Society* 2009; **57**: 482–485.

22. **Osbourn M, *et al.*** Outbreak of human metapneumovirus in fection in a residential aged care facility. *Communicable Disease Intelligence* 2009; **33**: 38–40.

23. **Fleming DM, Elliot AJ.** Respiratory syncytial virus: a sleeping giant? *European Respiratory Journal* 2007; **30**: 1029–1031.

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