A final concern is that McMANUS *et al.* [1] do not show whether spontaneously produced sputa and induced sputa were equally derived across all groups. Induction with hypertonic saline could dilute the Epstein–Barr virus DNA count. We are concerned that, particularly in the control group, induction of sputum production was needed.

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STATEMENT OF INTEREST

None declared.

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To the Editors:

The recent paper by McMANUS *et al.* [1] linking high levels of Epstein–Barr virus (EBV) to chronic obstructive pulmonary disease (COPD) is important as it appears to provide additional evidence supporting a connection between low serum 25-hydroxyvitamin D (calcidiol) and risk of COPD, and thus a possible simple way to reduce the risk of COPD. In an observational study, low pulmonary function was found to correlate with low serum calcidiol levels [2]. Statistically significant higher values of forced expiratory volume in one second (FEV₁) were found in: both sexes; those >60 yrs of age; White and Black subjects; subjects of any smoking status; subjects with a lack of asthma; those with or without bronchitis or emphysema.

There is additional support for a vitamin D–COPD link. Indeed, frequent cases of acute bronchitis increase the risk of COPD [3]. Respiratory syncytial virus (RSV) is an important risk factor for acute bronchitis. Solar ultraviolet (UV)B has been found to explain some of the seasonal and latitudinal variation in RSV activity. In a recent study, solar UVB explained 13% of the RSV activity in Miami (FL, USA), 5% in Buffalo (NY, USA) and 0.6% in Winnipeg (MB, Canada) [4]. The relevant action of vitamin D is the induction of human cathelicidin, LL-37 [5]. LL-37 is an important component of the innate immune system and vitamin D supplementation was demonstrated to reduce the risk of viral infections in a *post hoc* analysis of a randomised controlled trial.

Black postmenopausal women living in the state of New York (USA) had one-tenth the incidence rate of seasonal influenza and common cold when taking 2,000 IU·day⁻¹ of vitamin D₃ compared with those taking a placebo; those taking 800 IU·day⁻¹ had 40% the incidence rate of those taking a placebo [6].

There is growing evidence that EBV is a virus that is subject to the effects of vitamin D and LL-37. EBV is an important risk factor for multiple sclerosis [7]. The prevalence of multiple sclerosis increases with latitude in a manner related to wintertime solar UVB and vitamin D production. In the USA, those living at 28° N had 31% as much prevalence of multiple sclerosis as those living at 48° N, based on a study of veterans at the time of enlistment into World War II and the Korean conflict [8]. Summertime solar UVB doses are much higher from the Rocky Mountains (USA) to the west, than from the east of the Rocky Mountains at the same latitude due to higher surface elevation and thinner stratospheric ozone layer, and do not explain the observed prevalence findings. Multiple sclerosis is often preceded by infectious mononucleosis (IM) [9], and EBV is a risk factor for IM. Both IM and Hodgkin's lymphoma, another disease linked to EBV, have a peak incidence rate in spring, a time when calcidiol levels are lowest, amongst those <40 yrs of age [10].

It would therefore be worthwhile recommending increased serum calcidiol levels at the population level, especially in winter, in order to reduce the risk of chronic obstructive pulmonary disease. Those with chronic obstructive pulmonary disease may also be likely to benefit from increasing their serum calcidiol levels.

W.B. Grant

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STATEMENT OF INTEREST

None declared.

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From the authors:

We would like to thank A.W.J. Bossink and colleagues for their comments.

With regard to Epstein–Barr virus (EBV) serostatus, our laboratory has a diagnostic interest in EBV serology and our experience would indicate that for the age ranges in our published study [1] (*i.e.* both patients and controls) there will be 100% seropositivity for EBV. In Northern Ireland (UK), 60% of 10 yr olds are seropositive; in adults, this figure rises to >95% (unpublished data; P.V. Coyle, Regional Virus Laboratory, Belfast Health and Social Care Trust, Belfast, UK; personal communication).

Regarding the possible contamination of sputum samples with EBV DNA present in saliva, we have found that there is good correlation between EBV in lower and upper respiratory tract specimens, which is not consistent with contamination. We and other labs see little evidence of latent EBV when testing whole blood or white blood cells, making the presence of B-cells in sputum unlikely to be a confounding factor.

On the point of PCR being unable to differentiate between DNA derived from active viral replication or latent infection, as we were not detecting latency in B-cells (as previously noted) and as EBV causes a productive infection in epithelial cells, it follows current knowledge [2, 3] that we were measuring active viral replication. This also makes the determination of the number of B-cells in the sputum irrelevant.

The final issue regarding potential dilution of specimens with hypertonic saline is unlikely to be significant as previously published work has shown that induced sputum separated from saliva is similar to lower respiratory secretions expectorated spontaneously [4]. In the setting of our previously published study [1], any dilutional effect was negligible within the context of an assay determining viral load over six logarithms.

We would also like thank W.B. Grant for his comments in relation to vitamin D and chronic obstructive pulmonary disease. These comments raise several interesting points in this area and highlight the need for further prospective studies in this group of patients.

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STATEMENT OF INTEREST

None declared.

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Extensively drug-resistant tuberculosis: is its definition correct?

To the Editors:

Two articles by MIGLIORI and co-workers [1, 2], which recently appeared in the *European Respiratory Journal* (ERJ), may support the idea that the current definition of extremely drug-resistant tuberculosis (XDR-TB) [3, 4] is not the most adequate.

In recent years, XDR-TB has become a major concern as it leads to incurable TB in a significant proportion of patients [4, 5]. XDR-TB was first defined in March 2006 as multidrug-resistant TB (MDR-TB; resistance to isoniazid and rifampicin) plus resistance to at least three of the six second-line anti-TB drug groups (fluoroquinolones, aminoglycosides, polypeptides,